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EDITORIAL

Innovative development model for high quality elderly care: A study of "chain + virtual elderly care" services in Hengyang City

Heng-Fen Hu

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Abstract

Hengyang City faces challenges from rapid aging, including weakened family care and a shortage of resources. The "three social linkage" mechanism integrates community of practice, social organizations, and professional support to improve health services for the aged. However, issues like low smart device use and talent shortages persist. This study aims to optimize resource allocation and service efficiency through a "chain + virtual elderly care" model. This article explores the "three social linkage" mechanism and the integration of chain services with virtual elderly care models in Hengyang City. It examines three core elements: Resource integration, service collaboration, and professional support. The community coordinates resources and maintains databases of elderly care needs, while social organizations provide services and social workers design care plans. Data was gathered through case studies, interviews, and observations, focusing on smart technology integration and service outcomes. The study also evaluates cross-departmental data sharing, social worker training, and funding mechanisms, using performance indicators like service delivery time, user satisfaction, and resource use. The analysis of elderly care services in Hengyang City reveals key issues and improvements within the "three social linkage" mechanism. The three social linkage mechanism has facilitated better resource integration and service collaboration. Communities have created resource lists and service demand databases, improving coordination. Social organizations provide specialized services, and social workers conduct home visits to create personalized care plans. The virtual elderly care platform has enhanced service efficiency, with smart devices like bracelets enabling real-time health monitoring. The "chain + virtual elderly care" model in Hengyang has effectively addressed issues of scattered and outdated resources by integrating services through community hubs, standardized stations, and dynamic resource databases. Smart elderly care platforms, especially devices like wristbands, have improved service efficiency and emergency response.

Key Words: Health services for the aged; Resource allocation; Community of practice; Observation; Emergency

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Core Tip: This study aims to explore the construction path of the "chain + virtual elderly care" service model, by establishing a community resource integration mechanism and a smart service platform, to achieve precise identification of service needs and dynamic allocation of resources. The research focuses on addressing three core issues: How to break down departmental barriers and form a service synergy through the "three social linkage" mechanism, how to use information technology to improve service response efficiency, and how to build a sustainable elderly care service supply system. The research results can provide replicable experience samples for cities of the same type, as well as theoretical support for improving the grassroots social governance system, which has practical significance for promoting equalization of basic elderly care services.

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INTRODUCTION

China is undergoing rapid population aging, which is creating significant challenges for elderly care. A key issue is the weakening of traditional family caregiving functions, coupled with a shortage of institutional elderly care resources. This has resulted in an increasing demand for alternative care systems[1]. Hengyang City, located in Central China, is a typical example of this trend, with its elderly population exceeding the national average. It faces the phenomenon of "getting old before getting rich", where rapid aging outpaces economic development[2].

In Hengyang, elderly care services face prominent challenges, including resource dispersion, a mismatch between supply and demand, and outdated technology. Specifically, community day care centers are underutilized, and social organizations lack the capacity to meet the growing needs of the elderly population[3]. These problems highlight the limitations of traditional elderly care models, which are increasingly unable to adapt to the diverse needs of the aging population.

In response, Hengyang has pioneered the "three social linkage" mechanism, a collaborative model involving community platforms, social organizations, and professional support from social workers. This approach has been successfully implemented in Shigu District and particularly in Huangshawan Street, where it has integrated community resources and social organization efforts to provide a comprehensive elderly care system, including day care, cultural activities, and life services[4]. While promising, challenges such as low smart device adoption, lack of a unified data-sharing platform, and insufficient professional talent persist, limiting the model's full potential[5].

This study explores the development of the "chain + virtual elderly care" service model, which aims to address these challenges by establishing a community resource integration mechanism and a smart service platform. The goal is to enhance service efficiency through precise needs identification and dynamic resource allocation. The research focuses on three key issues: Breaking down departmental barriers to improve service synergy, using technology to enhance service response times, and creating a sustainable elderly care system. The findings can provide replicable models for similar cities and offer valuable insights into improving grassroots social governance and promoting equal access to elderly care services.

THEORETICAL BASIS FOR THREE SOCIAL LINKAGE AND VIRTUAL ELDERLY CARE SERVICES

Social governance mechanism of three social linkage and its application in elderly care services

As an important practical form of social governance innovation, the core of three social linkage lies in building a collaborative mechanism between communities, social organizations, and social work teams. This mechanism forms a governance pattern of "community stage setting, organization singing, and professional support" by clarifying the roles and complementary functions of the three parties. In the field of elderly care services, this linkage mechanism can effectively solve the problems of resource dispersion and delayed response in traditional service models, and provide institutional guarantees for building a new type of elderly care service system[6].

The specific operation of the social governance mechanism includes three key links: First, the resource integration mechanism, where the community leverages its territorial management advantages, coordinates basic information such as site facilities and service needs within its jurisdiction, and establishes a database of elderly care service resources. Second, there is a collaborative mechanism where social organizations undertake specific service projects based on their professional expertise. Social workers use professional methods to assess needs and design services, forming a complete

chain of service supply. Finally, there is a professional support mechanism that continuously improves the professionalization level of the service team through regular training, supervision, and evaluation. These three mechanisms are interconnected to ensure the quality control of the entire process of elderly care services, from demand identification to service supply[7,8].

In the practice of Hengyang City, the application of this mechanism presents three significant characteristics. One is the platform based operation mode, where the community elderly care service center serves as a physical carrier, integrating multiple functions such as day care, cultural entertainment, and rehabilitation nursing. For example, Shigu District achieves intensive use of service space through the construction of standardized functional rooms[9]. The second is the supply of specialized services. Social organizations rely on social work teams to carry out precise service matching, such as establishing service files for the elderly through household surveys, and designing personalized service plans for special groups such as disabled and empty nesters. The third is to ensure sustainable operation. The government stimulates the participation of social forces through policy tools such as purchasing services and tax incentives, while establishing a service effectiveness evaluation mechanism to ensure resource utilization efficiency[10,11].

The application value of this governance mechanism is fully reflected in the field of elderly care services. Through the resource hub role of the community, the elderly care resources that were originally scattered in departments such as civil affairs and health can be effectively integrated. Social organizations, with their flexibility and innovation, can quickly respond to the constantly evolving service needs of the elderly. The professional social work team significantly improves the standardization and accuracy of services through case management, resource linking, and other methods[12]. The exploration of Hengyang City shows that the three social linkage mechanism not only solves the fragmentation problem of traditional elderly care services, but more importantly, builds a governance system with multi-party participation and clear rights and responsibilities, laying an institutional foundation for the high-quality development of elderly care services[13].

Theoretical framework construction of chain service and virtual elderly care model

The integration and innovation of chain services and virtual elderly care models is essentially the reconstruction of the elderly care service supply system through the synergistic effect of resource integration mechanisms and information technology means. This theoretical framework includes three core dimensions: Resource chain integration, service process reengineering, and intelligent management closed-loop, which together constitute a new ecosystem of elderly care services that is "demand driven resource linkage intelligent response".

At the level of resource integration, the chain service mechanism relies on the role of community hubs to establish a "vertically connected and horizontally linked" resource allocation network. In the vertical dimension, policy guidance is used to achieve overall planning of elderly care resources at the city, district, and street levels, while in the horizontal dimension, service elements from departments such as civil affairs, health, and human resources are integrated. This chain structure effectively solves the drawbacks of scattered resources and repetitive construction in traditional services. For example, Shigu District integrates facilities such as day care and rehabilitation nursing through community elderly care service centers, forming a spatial layout of a "15 minute service circle". Social organizations, as service carriers, dynamically adjust service projects based on the needs of the elderly, while social work teams achieve precise resource matching through case management, forming a complete chain of "demand collection resource matching service delivery" [14].

The innovation of virtual elderly care model is reflected in the digital reconstruction of service processes. The online smart platform collects real-time health data and service needs of the elderly through intelligent terminals, and uses big data analysis to generate personalized service plans. The offline service team responds quickly according to system instructions, forming an operational mechanism of "online intelligent dispatching and offline professional services". This combination of reality and virtuality breaks through the temporal and spatial limitations of traditional elderly care. For example, Huangshawan Street achieves instant response to emergency calls through smart bracelets, and completes service appointments such as purchasing and delivering meals through an APP platform. Technological empowerment not only improves service efficiency, but also establishes a closed-loop management system that includes service evaluation, quality traceability, and risk warning through visual monitoring of the service process.

The practical value of the theoretical framework lies in building a multi-party collaborative sustainable development mechanism. As a resource integration platform, the community coordinates and coordinates basic elements such as venue facilities and policy support, social organizations leverage their professional advantages and are responsible for the operation and implementation of specific service projects, and the social work team uses professional methods to conduct needs assessment and service design[15]. The synergistic effect of the linkage between the three societies has been verified in the practice of Hengyang, for example, by establishing a cross-departmental data sharing platform, it has broken down data barriers such as basic information, health records, and service records of the elderly. By cultivating a professional social work team, the quality of professional services such as caring for disabled elderly has been significantly improved. This innovative model not only retains the territorial advantages of community elderly care, but also integrates the technological dividends of smart elderly care, providing theoretical guidance for solving the structural contradictions between supply and demand of elderly care services.

Methodology and data sources

The methodology for this study involved a mixed-methods approach, combining both qualitative and quantitative data collection techniques. To examine the "three social linkage" mechanism and the "chain + virtual elderly care" model in Hengyang City, we conducted in-depth case studies in key areas, such as Shigu District and Huangshawan Street, where the model has been implemented. Data were collected through semi-structured interviews with local government officials, community leaders, social workers, and elderly residents to gain insights into the operational dynamics and

challenges of the system. Additionally, field observations were made at community elderly care centers, social organization facilities, and through the use of smart elderly care devices like health monitoring wristbands. A survey was also administered to measure the satisfaction and needs of elderly service recipients, alongside an analysis of existing data on service provision, resource utilization, and technology adoption rates. This comprehensive data collection allowed for a detailed evaluation of the model's effectiveness, its impact on service delivery, and the barriers faced by both service providers and recipients.

Data collection

Semi-structured interviews were conducted with key stakeholders, including community leaders, elderly care providers, and policy-makers. These interviews provided in-depth insights into the operational challenges and successes of the program. Additionally, focus group discussions with elderly participants were held to capture their personal experiences with the services offered.

A stratified random sampling method was used to select participants for both surveys and interviews. The sample included individuals from various socio-economic backgrounds to ensure diverse representation, as well as key stakeholders involved in the elderly care model's implementation.

Data from the Hengyang City Civil Affairs Bureau, Health Department, and Social Security Bureau were accessed to provide baseline information on the city's elderly population and the available resources. This included records on service delivery, health outcomes, and resource allocation.

Information was collected from elderly care service stations that provided day care, rehabilitation, and emergency services, focusing on the number of beneficiaries, service types, and operational efficiencies.

By providing detailed descriptions of the methodology, data sources, and analytical methods, this editorial ensures that the conclusions drawn are firmly grounded in empirical evidence. The use of multiple data sources (official records, service providers, and smart device data) and analytical methods (statistical analysis and thematic analysis) strengthens the reliability of the findings.

Additionally, the citations used throughout the methodology and results sections will reference these data sources, ensuring that all evidence supporting the conclusions is traceable and transparent. For instance, when discussing the efficiency of smart wristbands, we will cite the specific survey data (*e.g.*, the 8-minute average emergency response time) and any relevant studies or reports that validate the impact of technology in elderly care.

This detailed approach to methodology and data analysis will ensure that the editorial maintains a high level of scientific rigor, providing a clear, evidence-based understanding of the elderly care model’s effectiveness and areas for improvement.

CURRENT SITUATION OF ELDERLY CARE SERVICES IN HENGYANG CITY AND PRACTICE OF THREE SOCIETY LINKAGE

Characteristics of population aging and demand for elderly care services in Hengyang City

There are three significant characteristics of population aging in Hengyang City. First, the degree of aging continues to deepen, with the growth rate of the elderly population significantly faster than the national average. The trend of aging is becoming increasingly prominent, and the proportion of elderly people over 80 years old is increasing year by year. Second, changes in family structure have led to a doubling of elderly care pressure, with the proportion of empty nest and solitary elderly continuing to rise, and traditional family caregiving functions significantly weakened. Once again, there is an uneven regional distribution, with a significantly higher density of elderly population in old urban areas compared to new urban areas. Some old communities are lagging behind in aging adaptation and facing a shortage of elderly care service facilities, exacerbating the pressure on service supply.

The survey on the demand for elderly care services shows that the service needs of the elderly present multi-level and differentiated characteristics. In terms of daily care, disabled and semi-disabled elderly people have an urgent need for professional nursing care, while ordinary elderly people are more concerned about the convenience of daily services such as meal assistance and cleaning. The demand for medical and health services is particularly prominent, with significant gaps in services such as chronic disease management, rehabilitation therapy, and emergency assistance. In terms of spiritual and cultural needs, over 60% of the surveyed elderly expressed feelings of social loneliness and strong expectations for cultural and sports activities, interest training, and other services. It is worth noting that obstacles in using smart devices have made it difficult for some elderly people to enjoy smart elderly care services, and the issue of digital divide needs special attention[16].

The analysis of demand structure reveals three key contradictions: First, there is a contradiction between standardized service supply and personalized demand, as existing service projects are unable to meet the differentiated needs of elderly people with different health conditions. Second, there is a contradiction between the administrative allocation of service resources and the market-oriented demand, with some community elderly care services experiencing a phenomenon of "emphasizing facility construction over operational management". The third is the contradiction between traditional service methods and the transformation of smart elderly care. The low usage rate of smart terminals restricts the improvement of service efficiency. Research has found that elderly people in old communities rely more on basic services such as community canteens and day care, while elderly people in newly built urban areas are more concerned about quality services such as cultural and entertainment, and living and elderly care.

The demand research provides important basis for the implementation of the linkage mechanism among the three societies. The practice of Huangshawan Street in Shigu District has shown that establishing service files for the elderly through community coordination can accurately identify the core needs of different groups. Social organizations, relying on professional evaluation tools, can categorize their needs into emergency assistance, life assistance, spiritual comfort, and other categories. The social work team conducts regular home visits, dynamically updates demand information, and adjusts service plans. This demand response mechanism effectively solves the problem of supply-demand mismatch in traditional services and lays the data foundation for building a chain service system. The current challenge that urgently needs to be overcome is how to transform scattered demand information into a systematic service directory, and how to achieve intelligent matching of demand and resources through virtual platforms.

Operational mechanism of three social linkage in Hengyang's elderly care services

The operation of the three social linkage mechanism in Hengyang's elderly care services presents a clear collaborative logic and operational path. As a basic platform, the community establishes a resource list and service demand database to achieve coordinated management of elderly care resources. Taking Huangshawan Street in Shigu District as an example, the community elderly care service center integrates elements such as activity venues, medical resources, and convenient facilities within its jurisdiction, forming six functional modules including day care, cultural entertainment, and life services, and dynamically updates service demands through grid management. This resource integration mechanism effectively solves the coordination problem caused by the dispersion of service elements in different departments in the past.

Social organizations, as service providers, form differentiated service supply based on their professional advantages. During operation, social organizations design personalized service plans for special groups such as disabled elderly and empty nest elderly by undertaking government purchased service projects. For example, some organizations specialize in providing rehabilitation nursing services, while others focus on organizing recreational activities for the elderly. The social work team plays a professional role in this process, establishing service files for the elderly through regular home visits, using case management methods to classify service needs into three categories: Emergency assistance, life assistance, and spiritual comfort, and developing corresponding service response processes. Specifically, it includes three key links: Demand collection, service matching, and quality supervision. Community grid members upload elderly service needs in real time through intelligent terminals, social organizations claim tasks based on service types and professional fields, and social workers are responsible for tracking the service process and evaluating its effectiveness. The practice of Qingshan Street has shown that this mechanism reduces service response time to within 30 minutes through standardized service process design, and establishes a service evaluation feedback system, forming a virtuous cycle of "demand service improvement". The government stimulates the participation of social forces through policy tools such as purchasing services and offering discounts on venue leasing, while establishing a cross-departmental joint meeting system to coordinate and solve resource allocation problems. The application of the virtual elderly care platform realizes the integration of online and offline services, with devices such as smart bracelets and one click pagers monitoring the health status of the elderly in real time. The big data analysis system automatically generates a heat map of service demand, guiding service resources to dynamically allocate to areas with concentrated demand. This operating mode not only retains the local advantages of community elderly care, but also integrates technological innovation in smart elderly care, providing sustained impetus for improving service efficiency[17].

Implementation effectiveness and bottlenecks of the existing chain + virtual elderly care model

The current chain + virtual elderly care model implemented in Hengyang City has achieved phased results, but still faces multiple challenges in actual operation. This model integrates community resources and builds a smart platform, initially establishing an online and offline linkage service system. In pilot areas such as Huangshawan Street in Shigu District, community elderly care service centers integrate daytime care, rehabilitation nursing, and other facilities to form a "one-stop" service station. Elderly people can book meal delivery, housekeeping, and other services through intelligent terminals. Social organizations rely on online platforms to achieve rapid response to service needs, and social work teams use electronic records to carry out precise service matching, significantly reducing service waiting time. Especially with the application of smart bracelets and other devices, the efficiency of emergency call response has been significantly improved, and children can also view the health status of the elderly in real time through mobile apps. However, there are still significant constraints in actual promotion. First, the depth of resource integration is insufficient, and some communities still have communication barriers when coordinating cross-departmental resources such as healthcare and home economics. The data sharing platform has not fully integrated the information systems of departments such as health and civil affairs. Second, there is a gap in the application of technology. Although a virtual elderly care service platform has been built, the usage rate of smart devices in old communities is low, and some elderly people still rely on traditional service methods due to operational difficulties. Once again, there is a shortage of professional talent reserves, and the social work team has knowledge gaps in new skills such as data analysis and intelligent device maintenance, which affects the improvement of service quality. In addition, the matching degree between service supply and demand still needs to be optimized, and some communities have a structural contradiction of surplus supply of rehabilitation nursing services and insufficient mental comfort projects. In terms of operational mechanism, the efficiency of cross-departmental collaboration needs to be improved. For example, when implementing smart elderly care in Qingshan Street, the lack of real-time sharing of medical data resulted in delayed response to health monitoring services. The sustainability of capital investment is also facing challenges, as it mainly relies on government purchasing services and the market-oriented operation mechanism is not yet mature. The service evaluation system still needs to be improved, and some communities have a phenomenon of prioritizing service quantity over quality, lacking unified service effectiveness evaluation standards. These bottlenecks constrain the sustainable development of service models and require

breakthroughs through institutional innovation and technological upgrades.

CONSTRUCTION AND IMPLEMENTATION PATH OF FOUR HIGH QUALITY INNOVATION DEVELOPMENT MODELS

Design of resource integration and collaborative innovation mechanism based on the three social linkage

In the process of integrating elderly care service resources, communities, social organizations, and social work teams establish a complete chain of "demand discovery resource matching service supply" through clear division of labor and collaboration. As a resource integration hub, the community relies on grid management to establish a dynamic resource database, which systematically collects information on elderly care facilities, medical resources, and convenient services scattered in departments such as civil affairs and health. The practice of Huangshawan Street in Shigu District has shown that by drawing a community elderly care service resource map, the distribution of facilities such as day care centers and rehabilitation therapy rooms can be visually displayed, providing visual support for optimizing resource allocation. The collaborative innovation mechanism includes three key links: The first is the demand response mechanism. The social work team divides the needs of the elderly into categories such as life care, medical care, and spiritual comfort through home visits and intelligent terminal feedback, forming a precise service list. Next is the resource scheduling mechanism, where social organizations claim tasks based on service types, and communities achieve intelligent matching between service providers and demanders through virtual platforms. For example, in the purchasing and delivery service, the system automatically sends orders to the nearest social organization service point, significantly reducing response time. Finally, there is a quality assurance mechanism that establishes a multidimensional evaluation system that includes service duration, user evaluation, and follow-up records to ensure traceability and quality control of the service process. This mechanism has three innovative points in implementation: The first is to establish a "chain response" service process, forming a closed-loop management from requirement identification to service completion; the second is to build a "virtual + physical" resource pool and achieve cross-community scheduling of service resources through online platforms; the third is to innovate the "social worker + volunteer" collaboration model, where professional social workers are responsible for core services and volunteers assist in cultural and entertainment activities, ensuring service quality and expanding service coverage. The case of Qingshan Street shows that this collaborative mechanism significantly improves the utilization rate of community elderly care service resources, especially the sharing and use of rehabilitation nursing equipment, effectively alleviating the pressure of insufficient professional care resources.

Optimization strategies for intelligent chain services and virtual elderly care platforms

In the optimization process of intelligent chain services and virtual elderly care platforms, it is necessary to focus on solving the effective connection between technology applications and service systems. First, the functional architecture of the virtual elderly care platform should be improved, and a full process management system of "demand collection intelligent analysis service delivery quality tracking" should be established. By upgrading smart terminal devices and integrating core functions such as health monitoring, emergency calls, and service appointments, such as the smart wristband piloted and promoted in Huangshawan Street, not only can real-time monitoring of elderly heart rate, location, and other data be achieved, but also the operation process can be simplified through voice interaction, effectively reducing the threshold for elderly users. In addition, a resource pool for elderly care services will be established at the community level, and physical resources such as day care centers, community health stations, and convenience supermarkets will be digitally labeled to achieve cross community resource scheduling through virtual platforms. For example, Qingshan Street can establish an online resource map to display the real-time availability of rehabilitation equipment in various communities, making it convenient for elderly people to make appointments and use them nearby. At the same time, data barriers between departments such as civil affairs and health should be broken down, and a sharing mechanism for basic information, health records, and service records of the elderly should be established to provide data support for accurate services. In terms of technological applications, a simplified version of the APP interface has been developed to address the difficulty of elderly people using smart devices, with added icon prompts and voice guidance functions. Simultaneously, a collaborative account for children should be established to facilitate remote assistance by family members. In terms of equipment maintenance, it is recommended to provide dedicated technical instructors in each community, regularly conduct training on the use of smart devices, and ensure service continuity by establishing a rapid equipment maintenance channel.

The findings from this study have significant practical implications for design, implementation, and improvement of elderly care models, both in Hengyang City and in similar contexts

Improvement of elderly care systems: The research highlights how resource integration through the "three social linkage" mechanism can provide a more efficient and coordinated care model. Practitioners and policymakers in other cities could adopt similar integration strategies, with a focus on community-based care delivery systems. This approach could reduce gaps in service availability and enhance accessibility for elderly individuals.

Technological adaptation in elderly care: The use of smart devices like wristbands and emergency response systems is a key innovation highlighted by this study. The practical implication of this finding is the need for widespread adoption of technology to improve emergency responses and real-time monitoring of elderly health. Healthcare providers should focus on further enhancing the accessibility and usability of these technologies to ensure that elderly users, particularly

those with cognitive impairments, can fully benefit from them.

Workforce development and training: The findings underscore the importance of improving the skills of social work professionals involved in elderly care. There is a clear need for specialized training programs in areas such as technological device management, elderly psychological support, and interdepartmental collaboration. Social work professionals and caregivers need continuous development to stay abreast of evolving technologies and to better address the psychological and emotional needs of elderly individuals.

Policy and interdepartmental coordination: The study highlights a crucial gap in data integration across departments (*e.g.*, health, civil affairs, and social security). The practical implication is the need for policymakers to prioritize the creation of unified digital platforms and data-sharing mechanisms that can foster a more coordinated approach to elderly care. This will enable better tracking of service delivery, health conditions, and overall elderly well-being, facilitating timely interventions.

In terms of future research, the study opens several pathways for further exploration and expansion of the elderly care model

Long-term impact evaluation: While this study provides a snapshot of the effectiveness of the "three social linkage" mechanism, a long-term evaluation is necessary to understand how sustainable the improvements are over time. Future studies should track the system's performance over several years to assess whether the improvements in emergency response times and service delivery persist and how they evolve.

Expanding the study to other regions: The research focused on Hengyang City, but its findings have potential implications for other regions. Future research could expand the study to different urban and rural areas, comparing how the "three social linkage" mechanism works in different contexts with varying socio-economic and infrastructural conditions. This could help determine the scalability and adaptability of the model to different regions and populations.

Technological advancements in elderly care: As technology continues to evolve, future studies should explore how emerging technologies [*e.g.*, artificial intelligence (AI), Internet of Things, and advanced health monitoring systems] can further improve elderly care. Research on smart homes, wearable health devices, and AI-assisted caregiving would provide additional insights into how technology can be integrated into elderly care models to enhance autonomy and quality of life for elderly individuals.

Evaluating social work education and training programs: Future studies could examine the effectiveness of vocational training programs in elderly care and whether specialized curricula for social work professionals in this field improve care outcomes. This could lead to the development of standardized curricula that integrate both technological proficiency and elderly psychological care into social work training.

Sustainable funding models for elderly care: A key area for future research is the financial sustainability of elderly care programs. Researchers should explore the potential for innovative funding models, including public-private partnerships and social impact investments, that can ensure the continuous operation and expansion of services. Investigating how to balance public funding with private sector contributions could provide a more sustainable financial foundation for the elderly care sector.

Study limitations

Data availability and quality: The study's reliance on data from local departments may limit the accuracy and completeness of the findings, particularly for long-term outcomes.

Limited scope of sample: The focus on Hengyang City may restrict the generalizability of the model to other regions with different demographic or infrastructural characteristics.

Lack of long-term evaluation: A longer-term assessment of the system's effectiveness and sustainability is needed to determine its ongoing impact.

Technology adoption by elderly users: The study did not delve deeply into the specific barriers that elderly individuals face in adopting and utilizing smart devices, which could affect the model's overall success.

Resource allocation and financial constraints: Financial sustainability and the allocation of resources for continued system expansion were not fully explored, which may pose a challenge for long-term implementation.

CONCLUSION

The "three social linkage" mechanism in Hengyang City's elderly care model has proven effective in addressing the fragmented service resources through community-driven integration. The application of smart devices, such as wristbands for emergency response, has also improved service efficiency. However, challenges remain, including data-sharing barriers, low utilization of smart technologies, and gaps in professional social work training. To overcome these issues, it is recommended that a city-level coordination mechanism be established for data integration, more accessible

smart devices and training programs be introduced, and a sustainable funding model be developed. By addressing these challenges, the city can ensure the long-term success and scalability of its elderly care services.

FOOTNOTES

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REVIEW

Cytoprotective effect of prostacyclin on hepatic ischemia-reperfusion injury

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Abstract

Hepatic ischemia-reperfusion injury is an important mechanism of liver failure that occurs in many clinical conditions, including massive hemorrhage, major hepatectomy and liver transplantation, and leads to poor outcomes. The underlying cellular and molecular reactions are extremely complex and not completely understood. Anaerobic metabolism, ATP depletion, intracellular acidosis, calcium overload, mitochondrial dysfunction, oxidative stress, activation of Kupffer cells and neutrophils, platelet aggregation, nitric oxide production, activation of the complement system and overexpression of cytokines and chemokines constitute the main pathophysiological actions and pathways for possible therapeutic strategies. Prostaglandins (PGs) are a group of biologically active lipid compounds called eicosanoids with many physiological activities. Prostacyclin (PGI_2) is a member of the PGs family with an unstable chemical structure and a very short half-life. PGI_2 has potent vasodilating activity, inhibits platelet activation and exerts anti-inflammatory effects. PGI_2 has been evaluated in chronic liver

disease as a mediator of hepatic stellate cell function, an antiproliferative and antifibrotic agent and a regulator of the hepatic microcirculation. In recent decades, the cytoprotective effects of PGI_2 analogs on hepatic ischemia-reperfusion injury have been experimentally and clinically studied. Moreover, the administration of synthetic PGI_2 analogs to patients who underwent liver transplantation produced very encouraging results. The downregulation of PGE_2 production, reduction of neutrophil aggregation in liver lobules, regulation of local microcirculatory homeostasis, improvement in mitochondrial function, alleviation of hepatic oxidative stress, suppression of the c-Jun N-terminal kinase and p38 cascades and downregulation of tumor necrosis factor-alpha and interleukin-1β production constitute some of the underlying physiological mechanisms of the beneficial effects of PGI_2 on hepatic ischemia-reperfusion injury. Thus, PGI_2 analogs appear to hold great promise for the management of hepatic ischemia-reperfusion injury, but further research is needed.

Key Words: Hepatic ischemia-reperfusion injury; Oxidative stress; Prostacyclin analogs; Prostaglandins; Liver transplantation; Liver graft dysfunction

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Core Tip: Hepatic ischemia-reperfusion injury is a critical event that affects the outcomes of liver surgery, transplantation and many other major clinical conditions. The reoxygenation of ischemic hepatocytes activates complex inflammatory processes, which lead to oxidative stress that has deleterious local and global consequences. Prostacyclin (PGI_2) is a well-known member of the prostaglandin family with potent vasodilative, platelet-inhibiting and anti-inflammatory effects. Several reports have detailed the cytoprotective effects of PGI_2 analogs on hepatic ischemia-reperfusion injury. In this review, we discuss the underlying mechanisms of hepatic ischemia-reperfusion injury and the potential hepatoprotective effects of PGI_2 analogs.

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INTRODUCTION

The liver is a critical organ for the homeostasis of the human body because it regulates many physiological processes, such as glycogen storage and energy metabolism, protein production, lipid and cholesterol metabolism, and bile excretion. Moreover, the functions of the liver include blood volume regulation and immune system support *via* the production of most immune factors, including cytokines, chemokines, growth factors and other signaling proteins. Additionally, several drugs are metabolized in the liver by a specific group of cytochrome P-450 enzymes. Finally, hepatic enzymes play key roles in the xenobiotic detoxification process because these enzymes convert toxic compounds into forms suitable for elimination[1,2]. Worldwide, liver failure is a common cause of high morbidity and mortality. The list of factors and conditions that cause liver failure is growing, and liver transplantation remains the only effective therapeutic option for these patients[3-5].

Ischemia-reperfusion injury is an important mechanism of liver failure after several clinical events, such as extended hepatic resection, massive hemorrhage, Budd-Chiari syndrome and liver transplantation[6]. The processes involved in hepatic ischemia-reperfusion injury are extremely complex and involve different types of liver cells, including numerous factors and mediators [cytokines, adhesion molecules, vasoactive agents and reactive oxygen species (ROS)][7-9]. The essential functions of the liver can be affected during hepatic ischemia-reperfusion injury in multiple ways, as shown in Figure 1.

Prostaglandins (PGs) are a group of biologically active lipid compounds that, in combination with leukotrienes (LTs), thromboxanes (TXs), lipoxins (LXs) and epoxyeicosatrienoic acids (EETs), are called eicosanoids. The chemoenzymatic synthetic pathway of PGs includes oxidized derivatives of 20-carbon polyunsaturated fatty acids, primarily arachidonic acid and cyclooxygenase (COX). PGs are widely distributed in nearly all human cells and tissues, but they are well known for having many biological actions[10-13].

PG has favorable effects on liver tissue, but the underlying mechanisms have not been completely defined[14]. Many studies have shown the cytoprotective activity of PG through direct or indirect signaling pathways[15]. The regulation of liver microcirculation, mainly *via* vasodilation, antioxidant effects and the modulation of the immune response, is considered critical for hepatocyte homeostasis[16,17].

Several studies have evaluated the effectiveness of PG analogs in adult and pediatric liver transplant patients. PGE_1 administration has been shown to improve the hepatic microcirculation status, prevent primary allograft nonfunction and reduce hepatic ischemia-reperfusion injury in general. Additionally, PGE_1 pretreatment downregulates the expression of adhesion and inflammatory mediators, resulting in the inhibition of platelet and leukocyte aggregation and a reduction in

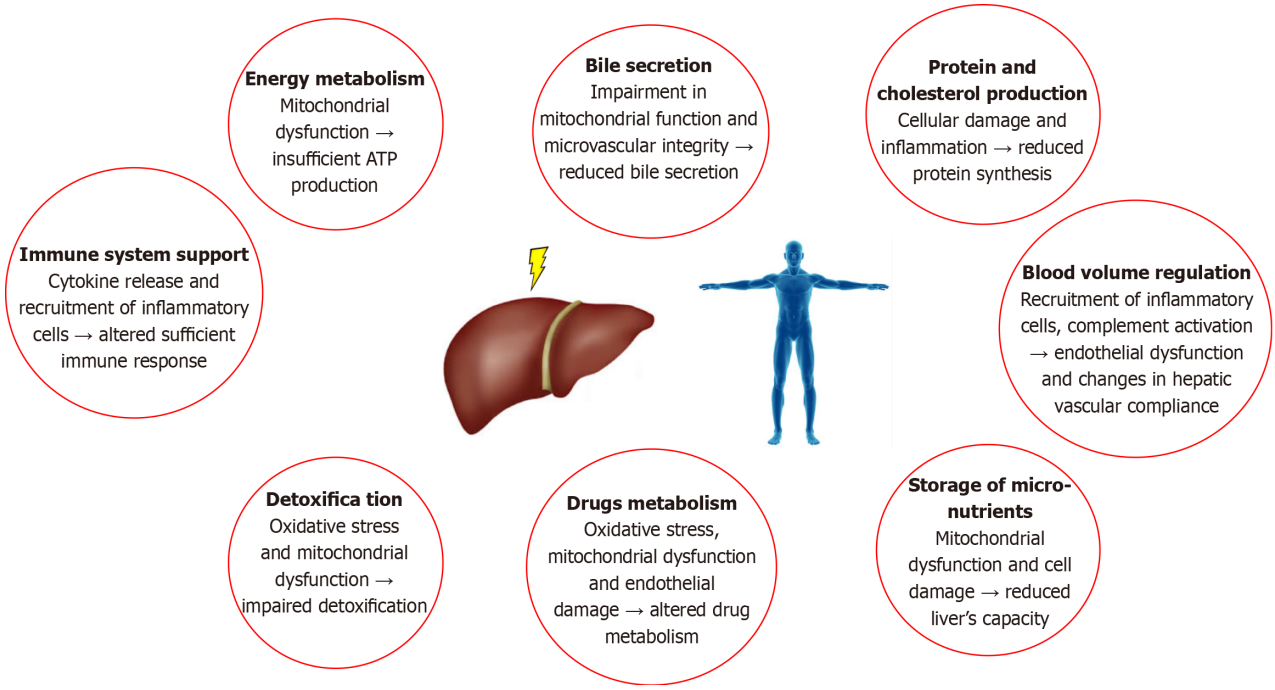


Figure 1 Main functions of the liver and how they are affected by ischemia-reperfusion injury.

hepatocytic degeneration[18-22]. Another eicosanoid, TXA_2, is a potent stimulator of platelet activation and aggregation; thus, its suppression leads to an attenuation of the inflammatory response and a reduction in the sinusoidal cell apoptosis rate. Moreover, recent studies have shown that the TX signaling pathway is involved in liver repair through the recruitment of macrophages to the injured hepatic tissue and increased transcription of growth factors[23,24].

Historically, PGs PGI_2 has been known to play a role in cardioprotection as an inhibitor of platelet activation and a vasodilator. Furthermore, it protects the heart from ischemia-reperfusion injury[25,26]. In addition, PGI_2 undoubtedly remains the most effective treatment for patients with pulmonary arterial hypertension[27]. However, increasing attention has been given to the cytoprotective and anti-inflammatory effects of PGI_2 analogs in the context of hepatic ischemia-reperfusion injury. Beraprost sodium is a PGI_2 analog with potential vasodilative, antiplatelet, anti-inflammatory and antioxidant activities. Inhibition of the P38 and c-Jun N-terminal kinase (JNK) signaling cascades with beraprost sodium preconditioning minimized the inflammatory response, apoptosis and autophagy processes[28]. Treprostinil is another PGI_2 analog with a stable structure, longer half-life and improved potency. Experimental and clinical data demonstrated the inhibition of platelet aggregation and proinflammatory cytokine production. Furthermore, hepatic oxidative stress and lipid peroxidation are attenuated after treprostinil administration, which reduces ischemia-induced hepatocyte injury[29-31].

Innovations in the field of liver surgery and the widespread use of vascular blockade for intraoperative bleeding control have made the liver particularly vulnerable to ischemia-reperfusion injury. The protective strategies mainly include specific intraoperative techniques and an adequate number of pharmacological agents. Here, we discuss the current knowledge of the mechanisms of hepatic ischemia-reperfusion injury and the potential cytoprotective effects of prostacyclin analogs.

HEPATIC ISCHEMIA-REPERFUSION INJURY

Despite progress in liver surgery, postoperative liver dysfunction continues to be an important and potentially fatal complication that is observed mainly after extensive hepatic resection and procedures in patients with reduced liver function or after liver transplantation. Hepatic ischemia-reperfusion injury remains one of the main causes of this complication[9,32-34]. This condition is characterized by complex cellular damage in a state of interruption of blood flow. Notably, the reperfusion of the ischemic tissue and the restoration of the oxygen supply exacerbate the degree of cellular injury. This injury has been described in various organs and systems because it is associated with several conditions, such as acute coronary syndrome, organ transplantation, limb injuries and sepsis[35,36].

Toledo-Petreya recognized this form of hepatocyte damage as clinically significant in 1975 during an experimental liver transplantation[37]. However, the term "hepatic ischemia-reperfusion injury" started being used much later, in the mid-1980s[38].

The complex blood supply of the liver in combination with its increased metabolic activity makes this organ extremely sensitive to circulatory disorders. The degree of cellular damage depends on the duration of ischemia-reperfusion. Additionally, several predisposing factors, such as diabetes mellitus, hyperlipidemia and arterial hypertension, contribute to atherosclerosis progression and affect the microcirculation. Disturbances in micronutrient homeostasis and energy

storage, as well as dysregulated detoxification and immune processes, lead to complex reactions that affect other organs and tissues and lead to multiorgan dysfunction syndrome. Hepatic ischemia-reperfusion injury remains a major cause of postoperative complications and worsened outcomes[38-42].

Hepatic ischemia-reperfusion injury can be categorized into warm and cold ischemia. Warm ischemia occurs during liver surgery or trauma, whereas cold ischemia is associated with organ storage before transplantation. The responsible mechanisms are extremely complex and involve multiple inflammatory mediators, cytokines, adhesion molecules, vasoactive factors and ROS, as shown in Figure 2. The significance of the overproduced molecules is summarized in Table 1. Because the liver circulation is disrupted, many reactions occur at the organelle level and stimulate cellular damage. The exposure of hepatocytes to low-oxygen conditions results in changes in the intracellular pH and a decrease in ATP production, causing a reduction in the intracellular energy level[6,9]. Excessive ROS and reactive nitrogen species production in mitochondria and intracellular calcium overload promote organelle destruction and cell death. The innate immune response includes the activation of Kupffer cells; the accumulation of circulating lymphocytes, neutrophils, platelets and monocytes; and hepatic macrophage differentiation[43-46]. A disruption of hepatic metabolism triggers an endogenous inflammatory cascade, which includes excessive cytokine and chemokine production, adhesion molecule expression and caspase-1 activation. The re-exposure of ischemic cells to high oxygen levels followed by blood flow restoration contribute to further hepatocyte injury through continued ROS generation[47-49].

Anaerobic metabolism, ATP depletion and acidosis

Impaired oxidative phosphorylation during ischemia results in the activation of anaerobic metabolism. Decreased ATP production and the intracellular accumulation of lactic acid and ketones almost always result in high anion gap metabolic acidosis[43,50]. As a response to the increased intracellular hydrogen ion concentration, the increase in Na+/H+ antiporter activity leads to the exchange of ions and an increase in the intracellular sodium concentration. The decreased activity of the ATP-dependent sodium-potassium pump further increases the intracellular sodium concentration, resulting in cell edema and death[51,52]. Moreover, diffuse cell edema affects microcirculatory structures and exacerbates ischemic damage.

However, acidic environments may also act to limit cell damage. Metabolic acidosis suppresses proteolytic enzyme and phospholipase activity and limits mitochondrial permeability transition pore (MPTP) function. Thus, during the reperfusion phase, a restoration of the intracellular pH leads to the activation of these enzymes, resulting in hepatocyte apoptosis and necrosis[53].

Intracellular calcium overload

Changes in intracellular calcium concentrations have emerged as important mechanisms of cellular damage because they lead to the activation of calcium-dependent enzymes. Under normal conditions, intracellular calcium homeostasis is based on ATP-dependent processes and reactions. When ischemia occurs, an increase in the intracellular sodium concentration induces sodium-calcium exchange, resulting in increased transfer of calcium ions inside the cells[54-56]. Cytoplasmic calcium overload subsequently stimulates calcium exchangers in the mitochondrial membrane. In combination with MPTP dysfunction, this action leads to the migration of calcium ions into the mitochondria[57]. Overall, calcium overload results in the activation of numerous enzymes, such as calpains, protein kinase C, phospholipase C, xanthine dehydrogenase and calcium-dependent proteases, which further affect the stability of the cell membrane and intracellular structures[53,58]. Eventually, the release of proapoptotic factors in the cytoplasm due to ischemia results in the acceleration of cell death processes[59]. The experimental administration of calcium channel blockers in animal models of hepatic ischemia-reperfusion injury assisted in the recovery of mitochondrial damage and hepatocyte functions, which indicates the importance of the calcium overload theory[60].

The role of mitochondria

Mitochondria are the center of cellular energy metabolism and redox homeostasis. Nonetheless, mitochondrial function deteriorates in the hypoxic environment. During hepatic ischemia-reperfusion injury, increased intracellular concentrations of sodium, hydrogen, and calcium ions contribute to mitochondrial dysfunction and lead to MPTP formation[58]. The removal of damaged mitochondria through mitophagy is very important for the maintenance of intracellular homeostasis because mitochondria are responsible for both increased ATP consumption and increased ROS production [61,62]. Disruptions in mitophagy during ischemia-reperfusion injury are associated with mitochondrial dysfunction and the disruption of the oxidative phosphorylation pathway. In connection with increased mitochondrial membrane permeability, these processes are responsible for ATP depletion, resulting in cell death[63,64].

Oxidative stress and the roles of Kupffer cells and neutrophils

ROS are produced by normal physiological processes, including anaerobic metabolism, oxidative phosphorylation, lipid degradation and the inflammatory response. Accordingly, cells have evolved endogenous antioxidant systems, such as catalase, glutathione peroxidase and superoxide dismutase[65,66]. Increased production of ROS [hydroxyl radicals (·OH), superoxide anions ($\cdot O2^-$), and hydrogen peroxide (H_2O_2)] has a toxic effect on hepatocytes. In the reperfusion phase, the excess ROS levels exceed the antioxidant capacity of hepatocytes, resulting in oxidative stress. In the liver, the main sources of these molecules are the mitochondrial membranes of Kupffer cells, neutrophils and monocytes. However, the metabolic reactions involve nicotinamide dinucleotide phosphate adenine oxidase (NADPH) and xanthine oxidase[67-69]. A low oxygen supply induces the activation of transcriptional regulators, such as hypoxia inducible factor-1, nuclear factor kappa B (NF-κB), activator protein 1 and stress-activated protein kinase, triggering further ROS production and cellular damage, including changes in enzyme activity, membrane lipid peroxidation and DNA damage[70]. The

Table 1 Overproduced molecules and its consequences in hepatic ischemia-reperfusion injury

Number	Molecule	Effect
1	Tumor necrosis factor α	Central mediator with multifactorial effect
2	Interleukin-1α	Mediator of neutrophil infiltration
3	Interleukin-1β	Induction of prostaglandin synthesis, enhancement of T-cell and neutrophil activation and cytokine production
4	Interleukin-12	Induction and development of hepatic ischemia-reperfusion injury
5	Interferon-γ	Increases or reduces neutrophil accumulation in a dose-depend manner
6	Damage-associated molecular patterns	Pro- and anti-inflammatory mediators that promote tissue damage
7	Intercellular adhesion molecule 1	Promotes neutrophil accumulation
8	Vascular cell adhesion molecule 1	Mediates inflammation and promotes neutrophil migration
9	P-selectin	Promotes neutrophil and platelets adhesion
10	Transforming growth factor-β	Promotes vessel wall inflammation and increase vascular permeability
11	Vascular endothelial growth factor	Promotes T lymphocyte, macrophage and neutrophil accumulation
12	Plasminogen activator inhibitor 1	Promotes neutrophil accumulation and suppresses fibrinolysis
13	Nitric oxide	Prevents or promotes cell damage depending on NO synthesis processes
14	Endothelin-1	Vasoconstriction
15	Combination of released factors	Heart-kidney damage, systematic inflammatory response syndrome SIRS, multiple organ dysfunction, death

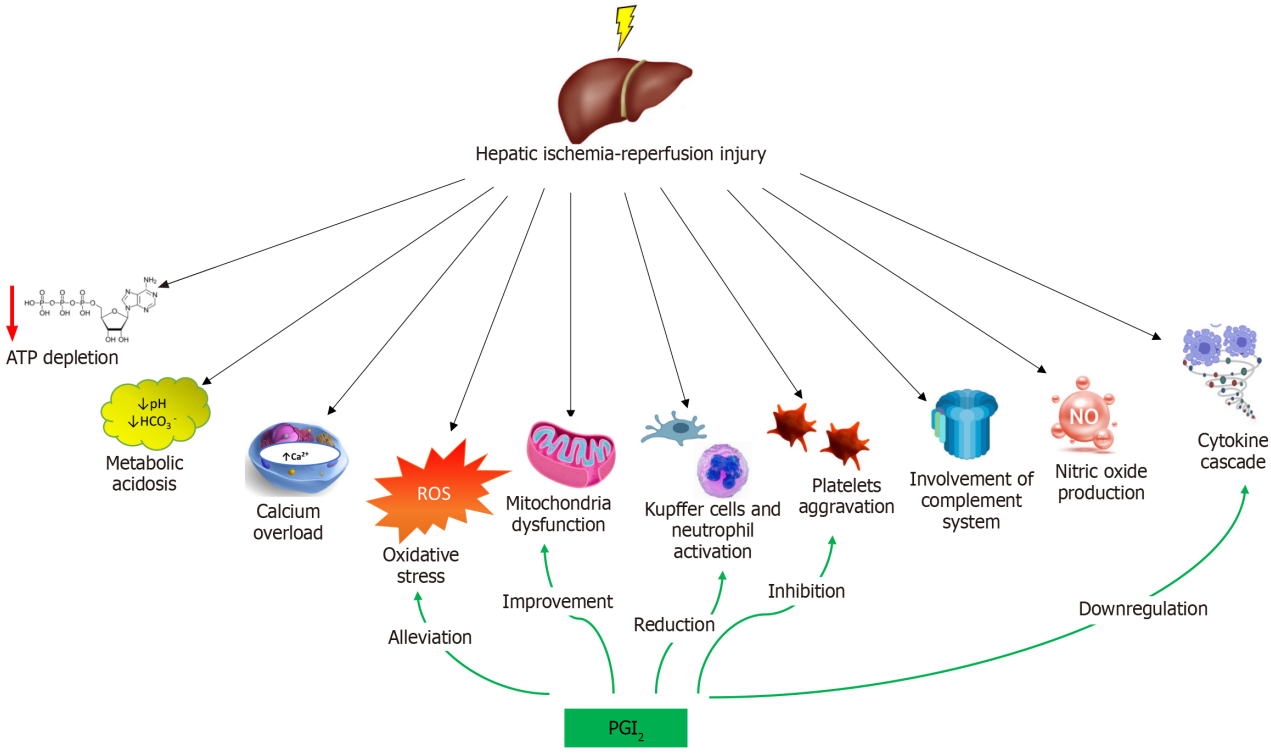


Figure 2 Mechanisms of hepatic ischemia-reperfusion injury and prostacyclin effect. PGI_2: Pprostacyclin; ROS: Reactive oxygen species.

abovementioned mechanisms, combined with endothelial cell damage and subsequent microcirculation disturbances, induce hepatocyte death[71,72].

Kupffer cells and neutrophils contribute to hepatic ischemia-reperfusion injury at different stages. Hepatic ischemia-reperfusion injury can be divided into two phases: The initial phase (< 2 hour after reperfusion) and the late phase (6-48 hour after reperfusion). The early phase is characterized by the rapid activation of Kupffer cells, whereas the late phase processes are mediated by accumulated neutrophils[35,73]. Activated Kupffer cells release proinflammatory factors, such

as ROS, tumor necrosis factor-α (TNF-α), interleukin (IL) 1β and damage-associated molecular patterns (DAMPs). In addition, the activation of sinusoidal endothelial cells and increased expression of intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) promote the migration and adhesion of neutrophils and CD4+ T cells[74-76]. Accumulated and activated neutrophils express oxidants, elastases and proteases, resulting in drastic increases in vascular permeability, edema and microvascular thrombosis. Furthermore, DAMPs are released during the reperfusion phase; they act as a complex cascade of pro- and anti-inflammatory mediators and promote tissue damage [44].

Activated neutrophils generate superoxide anions and subsequently produce hydrogen peroxide and myeloperoxidase [77]. Hydrogen peroxide is a strong agent with direct oxidative properties. However, myeloperoxidase converts hydrogen peroxide to hypochlorous acid, which also causes cell damage.

PGI_2 is an important PGs with powerful vasodilative activity and is a potent inhibitor of neutrophil activation. Therefore, endothelial PGI_2 might have a protective effect on hepatic ischemia-reperfusion injury by maintaining proper microcirculation and preventing neutrophil-induced endothelial cell damage. Neutrophil elastase, a protease released from activated neutrophils, reduces PGI_2 production by inhibiting nitric oxide (NO) synthase (NOS), thereby contributing to cell damage in the context of hepatic ischemia-reperfusion injury[78,79].

Platelets

Platelets play a very important role in hepatic ischemia-reperfusion injury because they produce a variety of factors, such as cytokines, growth factors [transforming growth factor-β; vascular endothelial growth factor (VEGF) A], serotonin, TXA_2, and plasminogen activator inhibitor (PAI-1)[80]. When endothelial damage occurs, the release of these factors results in a microcirculatory obstruction due to their strong vasoconstrictive effect. In addition, PAI-1 suppresses fibrinolysis and downregulates the liver regeneration process by inhibiting urokinase-like plasminogen activator[81]. Finally, platelets release NO, which reacts with superoxide anion and forms peroxynitrite anion ($ONOO^-$), an oxidative agent. Peroxynitrite interacts with lipids, DNS and proteins with direct or indirect pathways, committing cells to apoptosis or necrosis[82,83].

Role of the complement system

Studies of the hepatic ischemia-reperfusion process have increased our understanding of the role of the complement system, which appears to interfere with most of the pathophysiological mechanisms of the syndrome. The complement cascade mediates both ischemia-reperfusion injury pathways and liver regeneration[84]. The activation of the complement system results in the formation of biologically active, potent inflammatory mediators, such as C3a and C5a and the membrane attack complex (MAC)[85]. C3a and C5a promote cytokine production, neutrophil accumulation and degranulation. Additionally, they induce smooth muscle contraction, activate Kupffer cells, stimulate histamine release and increase vascular permeability[86,87]. The complement factor iC3b, which is formed by the cleavage of C3b by Factor I, mediates the binding of neutrophils to endothelial cells through CD11b/CD18, a member of the β2 integrin family.

C5b-9 (MAC) activates the transcription factor NF-kB, accelerating the expression of genes encoding various proinflammatory molecules, including adhesion molecules (ICAM-1 and VCAM-1), P-selectin and E-selectin. Moreover, C5b-9 increases the secretion of the chemotactic cytokines IL-8 and MCP-1 by human endothelial cells. The vascular microcirculation appears to be disturbed in the presence of C5b-9, resulting in a decrease in the tissue blood supply[88,89]. Finally, the MAC leads directly to cell lysis and death by disrupting the cell membrane, which has a variety of lipid compositions [84,90,91].

Roles of NO and endothelin

NO is a signaling molecule involved in many physiological biochemical reactions. It is synthesized from L-arginine and oxygen by NOS[90]. Three different NOS isoforms are known: Neuronal nNOS, endothelial eNOS and inducible iNOS. During hepatic ischemia-reperfusion injury, NO can either prevent or promote cell damage. A recent study revealed that NO can have either a positive or a negative effect during the early phase of ischemia-reperfusion injury and a protective effect in late stages[92,93]. NO derived from eNOS exerts a hepatoprotective effect by promoting vasodilation and improving the hepatic microcirculation, neutralizing ROS, preventing leukocyte adhesion, reducing the inflammatory response and inhibiting thrombus formation. NO derived from iNOS in the reperfusion phase leads to excessive cytokine and ROS production, which results in endothelial dysfunction and exacerbates hepatocellular injury[94,95]. Moreover, the continuous activation of iNOS leads to the maintenance of inflammatory reactions and further local and global damage. In general, NO participates in a variety of reactions, such as platelet and macrophage aggregation, the regulation of vasodilation and microcirculation, modification of the ATP level, caspase inhibition, a reduction in oxidative stress through respiratory chain inhibition, and the maintenance of appropriate glutathione levels. As a major mediator of the immune response, NO inhibits the secretion of many proinflammatory cytokines (TNF-α, IL-1β, IL-1α, and IL-12) and regulates the innate and adaptive immune systems[93,96,97]. In addition, NO downregulates LTsC4 synthase production by inhibiting the NF-κB pathway and limits the secretion of apoptosis-related genes such as Bax and Bcl-2[93,98]. Under certain circumstances, NO may delay or promote neutrophil apoptosis, depending on the context. iNOS-derived NO prolongs neutrophil survival by activating the PI3K/Akt signaling pathway, inhibiting caspase-3 and caspase-9 and contributing to inflammatory reactions. Conversely, the promotion of neutrophil apoptosis is often associated with a lower proportion of eNOS-derived NO, which induces mitochondrial dysfunction, leading to the activation of caspase-dependent apoptosis and the suppression of NF-κB activity[94]. Finally, NO can be converted to $ONOO^-$, which causes cellular damage through lipid peroxidation, inhibition of the mitochondrial respiratory chain and modification of the levels of nitrityrosine, an indirect marker of oxidative stress[99,100]. However, NO expression should be balanced to minimize the negative effect and to contribute to the attenuation of hepatic ischemia-reperfusion injury.

Endothelin-1 is a potent vasoconstrictive agent produced by endothelial and hepatic stellate cells to prevent liver injury [101]. The balance between endothelin and NO levels plays a pivotal role in regulating the hepatic microcirculation. Ischemia is an important stimulus for endothelin production, resulting in a disturbance in the balance of vasoregulatory factors. An increase in endothelin levels promotes vasoconstriction, hepatic sinusoidal dilatation, increased intrahepatic vascular resistance, enhanced endothelial interactions and portal hypertension[102,103].

Cytokines and chemokines

Reperfusion of the ischemic hepatic tissue triggers excessive cytokine release, which accelerates the inflammatory response. TNF-α represents a major mediator of both the local and global consequences of hepatic ischemia-reperfusion injury[40,104]. TNF-α, which is produced by numerous cell types in response to inflammatory stimuli, has been shown to modulate multiple signaling pathways with wide-ranging downstream effects[105-107]. Specifically, TNF-α binds to receptors on the surface of hepatocytes, causing the production of epithelial neutrophil-activating protein 78 and ROS. It also activates the nuclear factors NF-κB, mitogen-activated protein kinase (MAPK) and JNK. The abovementioned mediators directly cause hepatocyte dysfunction. In addition, TNF-α upregulates the expression of the chemokines ICAM-1, VCAM-1 and P-selectin. Several studies have shown that TNF-α inhibitors protect the liver from ischemia-reperfusion injury by neutralizing the inflammatory response[48,108].

T cells and natural killer T cells produce interferon-γ (IFN-γ), which affects the inflammatory response in various ways by increasing or reducing neutrophil accumulation in a dose-dependent manner[109]. In addition to TNF-α and IFN-γ, numerous other cytokines have been found to be involved in hepatic ischemia-reperfusion injury. Several ILs (IL-1β, IL-6, IL-10, IL-12, IL-13, and IL-23), VEGF and hepatocyte growth factor (HGF) are notable factors.

IL-1β mediates NO synthesis *via* protein kinase (Akt) and iNOS, whereas the activation of the nuclear factor NF-κB increases neutrophil migration and adhesion. Moreover, the IL-12 and IL-23 increase TNF-α production. Furthermore, IL-10 and IL-13 produced by Kupffer cells and T cells play important roles in reducing hepatocellular damage and promoting liver regeneration. The protective effects of IL-10 and IL-13 are mediated by the upregulation of transmembrane molecules (Bcl)-2/bcl-x and heme oxygenase and the downregulation of NF-kB, IL-2, IL-1b, MIP-2, IFN-γ, and E selectin[110,111]. VEGF, which is produced by Kupffer cells, T lymphocytes, sinusoidal cells and hepatocytes, plays dual roles in hepatic ischemia-reperfusion injury. An increase in the VEGF concentration during hypoxia increases TNF-α, INF-γ, MCP-1 and E-selectin secretion, resulting in T lymphocyte, macrophage and neutrophil accumulation. In contrast, exogenous VEGF administration has a favorable effect on hypoxia resolution *via* iNOS production. HGF is produced primarily by Kupffer cells and increases hepatocyte DNA synthesis, cell proliferation, and glutathione expression (which is decreased in the ischemic phase), decreases ICAM-1 secretion and inhibits neutrophil accumulation. HGF plays a vital role in the initial stage of liver repair[112,113].

Chemokines are low-molecular-weight proteins that stimulate neutrophil recruitment. During hepatic reperfusion, high levels of the ELR+ CXC subclass (based on the presence of the amino acid sequence Glu-Leu-Arg) are produced and contribute to neutrophil activation. This robust chemokine release leads to the recruitment of large numbers of immune cells into injured tissue and inflammation-mediated cytotoxicity[113]. The neutralization of ELR+ CXC chemokines significantly reduces inflammatory cell accumulation and alleviates hepatocellular damage[73,114-117].

Notably, studies investigating hepatic ischemia-reperfusion injury face several methodological limitations, which can affect the interpretation of their findings. Key points include the variability in experimental models, a focus on an isolated type of ischemia (warm or cold), modifications in the duration and design of surgical procedures, and a lack of approved criteria to evaluate liver damage. Moreover, *in vivo* models may more thoroughly demonstrate systemic reactions and hemodynamic changes, which are absent in isolated hepatocyte lines (*in vitro* studies). The reliance on animal models introduces several limitations due to species-specific differences in immune system reactions, drug pharmacokinetics and pharmacodynamics, metabolism and the expression of various molecules, such as complement proteins or PGI_2 receptors. In addition, the translation of experimental study findings to human pathophysiology may be challenging, as many patients with liver disease have comorbidities, which are not always represented in animal models. The abovementioned methodological limitations in standardized protocols, improved experimental models and comprehensive outcome evaluations must be addressed to make progress in identifying effective therapeutic strategies and to advance the interpretation of research data related to hepatic ischemia-reperfusion injury.

PGs

PGs are 20-carbon hydroxyl fatty acids that regulate many physiological processes, including immune cell activation, platelet aggregation, neurotransmitter release and kidney function. PGs are synthesized from arachidonic acid and cleaved from cell membrane lipids. The enzymatic oxidation of arachidonic acid is catalyzed by COX and 5-lipoxygenase, resulting in the synthesis of PGs and LTs, respectively. Specifically, the two isoforms of COX (COX-1 and COX-2) activate a two-step synthetic process, first generating PGG_2 from arachidonic acid and then reducing the 15-hydroperoxy group to form PGH_2. Subsequently, cell-specific PG synthases catalyze the conversion of PGH_2 to biologically active metabolites [118-121]. First, PGs were discovered independently in human semen in 1935 by the Swedish physiologist Ulf von Euler and the British physiologist M. W. Goldblatt. PGs are a biologically important group of fatty acids called eicosanoids. Other classes include LTs, TXs, LXs and EETs (as shown in Figure 3)[122,123].

The major classes of PG are known as PGA, PGB, PGD_2, PGE_2, PGF_2, and PGI_2 (prostacyclin). The differences among the classes are based on the chemical structure, particularly the nature of the 5-membered ring functionalities, as well as the number and location of side-chain double bonds[10,124,125]. PGs have been detected in nearly all human cells and tissues. They are well known for possessing a wide variety of biological actions, including homeostasis, activation/inhibition of platelet aggregation, thrombosis, glomerular filtration, ovulation, maintenance of pregnancy and initiation of labor, inflammatory mechanisms, vascular tone regulation, hormone level regulation, modulation of the immune

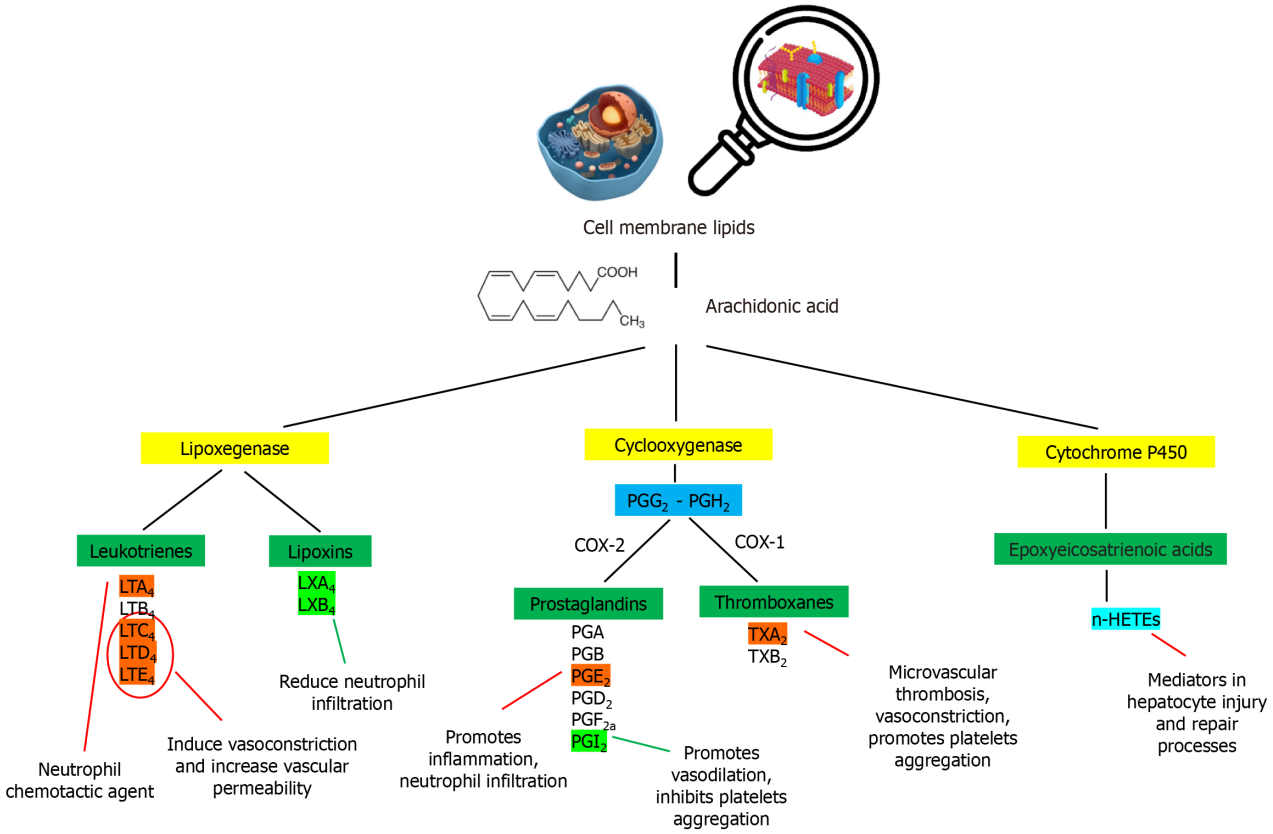


Figure 3 Simplified eicosanoids synthetic pathway and their role in hepatic ischemia-reperfusion injury.

response, and even more local reactions[126,127]. PGs bind to cell surface membrane molecules known as PG receptors to exert their biological actions. All PG receptors are rhodopsin-like G protein-coupled receptors that respond to all active PGH_2 metabolites, with some differences in action. Nine categories of PG receptors are currently known, and their classification is based on the PG and signaling pathways that they regulate (DP_1, DP_2, EP_1, EP_2, EP_3, EP_4, FP, IP, and TP)[119,128,129].

PROSTACYCLIN

PGI_2 is a member of the PG family with an unstable chemical structure at physiological pH. PGI_2 is a fragile molecule with a very short half-life (2-3 minutes) and rapidly forms the biologically inactive hydration product 6-keto- PG F1α[130]. In addition to other members of the PG family, PGI_2 is synthesized from cell membrane lipids derived from arachidonic acid, mainly through the COX-2 and prostacyclin synthase catalysis pathways[131]. PGI_2 is a potent inhibitor of platelet aggregation and activation and an effective vasodilator. Vascular smooth muscle cells and endothelial cells are the main sources of PGI_2 production in the human body, where it is activated by a paracrine signaling cascade that involves the prostacyclin receptor (IP). Specifically, a cell membrane receptor coupled with a GS-type protein binds PGI_2, resulting in the simulation of cyclic adenosine monophosphate (cAMP) production[132-134]. By acting as a second messenger (an action that occurs within cells), cAMP modulates a variety of biological processes. In vascular smooth muscles, cAMP mediates relaxation and inhibits proliferation, whereas in platelets, it reduces activation and thrombosis *via* the downregulation of calcium-associated pathways[135]. In this context, PGI_2 interacts with a system consisting of eNOS-NO-guanylate cyclase-cyclic guanosine monophosphate[136,137]. Notably, TXA_2, another arachidonic metabolite, acts as a physiological antagonist of PGI_2 by stimulating platelet aggregation and vasoconstriction[138]. Several reports have shown that changes in the PGI_2/TXA_2 ratio contribute to the development of endothelial dysfunction and atherosclerosis, as well as the progression of diabetes, pulmonary and systemic hypertension and renal dysfunction[139].

As mentioned above, PGI_2 has a chemically unstable structure and degrades rapidly into stable but biologically inactive metabolites. The structures of PGI_2 synthetic analogs are more stable, have longer half-lives and have improved potency. These analogs are used intravenously, subcutaneously or by inhalation as potent vasodilators, mainly in patients with pulmonary hypertension, Raynaud's syndrome or limb ischemia[140,141]. Recent studies have described the cytoprotective effect of the PGI2-cAMP pathway in endothelial cells[142,143]. Furthermore, PGI_2 enhances endothelial cell function and promotes angiogenesis in the ischemic environment by supporting the upregulation of NADPH oxidase 4 in cells[144]. The effects of PGI_2 are summarized in Table 2.

Table 2 Prostacyclin effects (IP receptors)

Number	Prostacyclin effects
1	Inhibition of platelets aggregation
2	Vasodilation
3	Inhibition of platelets adhesion
4	Angiogenesis
5	Reduction of myo-vascular remodelling
6	Inhibition of proliferation
7	Reduction of fibroblast migration
8	Reduction of cytokine release
9	Reduction of lipid peroxidation
10	Downregulation of adhesion molecules and growth factors
11	Inhibition of apoptosis
12	Reinforcement of endothelial cell function
13	Regulation of lipid metabolism

Protective role of prostacyclin in liver disease

PGI_2 appears to have important biological functions in chronic liver injury progression. It acts as a local mediator to regulate hepatic stellate cell function by binding to specific cellular receptors[144]. In addition to hemodynamic variations in portal hypertension, the *in vitro* administration of PGI_2 has been shown to have antiproliferative and antifibrotic effects on human hepatic stellate cells by inhibiting fibroblast migration and decreasing TNF-α production[145,146]. Furthermore, PGI_2 analogs have been shown to have hepatoprotective and antiapoptotic effects[147].

In fact, the management of the hepatic microcirculation by preventing liver sinusoidal vasoconstriction, in combination with the downregulation of inflammatory cell migration and hepatic stellate cell activation and proliferation, make PGI_2 an important factor in delaying liver fibrosis[148]. In light of the scientific evidence, PGI_2 analogs have been suggested as new therapeutic options for the management of patients with chronic liver disease, such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis and alcohol-related liver disease[144]. In agreement with previous findings, PGI_2 inhibition during acute liver injury exacerbated hepatic cell damage. Although the underlying mechanisms are not fully understood, the cytoprotective effect of PGI_2 may be related to vasodilation and the maintenance of hepatic perfusion, as well as a reduction in lipid peroxidation and the release of inflammatory mediators[149-151]. An analysis of gene expression revealed increased expression of hepatic SIRT1 protein and peroxisome proliferator-activated receptor-α after experimental beraprost sodium administration to mice. Specifically, the activation of the SIRT1 pathway leads to the attenuation of hepatic steatosis and the regulation of lipid metabolism[152]. These interesting findings concerning the hepatoprotective effect of PGI_2 require further research to verify its potential therapeutic use in the management of patients with progressive liver disease.

Prostacyclin in hepatic ischemia-reperfusion injury

The benefits of PGI_2 analogs for hepatic ischemia-reperfusion injury have been studied for nearly 40 years since the first study was published in 1982, where 24- and 48-hour canine liver preservation in solutions containing PGI_2 led to successful orthotopic liver transplantation[153]. Moreover, subsequent studies verified the previous findings, resulting in the clinical application of PGI_2 in optimizing cadaveric and living organ donation[154-156]. Other investigations focused on elucidating the underlying hepatoprotective mechanisms (Figure 2) along with attempting to integrate PGI_2 analogs into therapeutic options.

PGI_2 analog (OP 2507) administration in complete warm ischemia of the animal liver had a hepatoprotective effect by downregulating PGE_2 production in the reperfused liver and ameliorating serum transferase release[157]. These findings were supported by another animal model in which TXA_2 inhibition by the synthase inhibitor OKY-046 increased endogenous PGI_2 production, resulting in the prevention of liver damage[158]. Undoubtedly, the PGI_2/TXA_2 balance is very important for microcirculatory homeostasis because of its antagonistic effects. Endothelium-derived PGI_2 is well known for its potent vasodilating, vasoprotective and thromboresistive activities, along with its ability to inhibit platelet aggregation, whereas TXA_2 causes vasoconstriction and platelet activation and triggers vascular inflammatory processes [119,139,159-161]. Several reports have indicated that the dysregulation of the PGI_2/TXA_2 balance is responsible for the development of endothelial dysfunction, systemic and pulmonary hypertension, diabetes progression, a decrease in the glomerular filtration rate and tumor growth[162-166].

Liver transplantation is the only therapeutic option for patients with end-stage liver disease and has high 5- and 10-year survival rates. Despite the continuous improvement in surgical techniques, a significant number of patients still suffer from postoperative graft dysfunction[167,168]. Severe hepatic ischemia-reperfusion injury can be responsible for early graft dysfunction and may require retransplantation[169]. Therefore, operative and pharmacological approaches to

ameliorate graft postreperfusion injury are urgently needed. Experimental preconditioning with epoprostenol (a PGI_2 analog) in a rat liver transplantation model resulted in improved perfusion of the liver sinusoids, increased bile production and reduced leukocyte aggregation in liver lobules and postsinusoidal venules[170]. Moreover, a prospective randomized placebo-controlled study that investigated the effects of PGI_2 on postoperative graft function following clinical liver transplantation was published in 2000[171]. Patients who received continuous PGI_2 at a dose of 4 ng/min per kg until the 7th postoperative day presented improved hepatic-splanchnic oxygenation. Additionally, these findings are supported by previous reports that suggested the use of stable PGI_2 analogs for liver allograft preservation prior to transplantation along with the treatment of primary liver graft nonfunction[172,173]. Furthermore, Zardi *et al*[174] successfully improved hepatic perfusion with iloprost (another PGI_2 analog) in 15 patients with systemic sclerosis to prevent vascular complications. Specifically, a continuous infusion of iloprost for 5 days increased the portal flow velocity and portal flow volume, as confirmed by color Doppler ultrasonography, resulting in increased local microcirculatory homeostasis. However, PGI_2 appears to have dose- and phase-dependent effects on hepatic perfusion and microcirculation[175-177].

In the context of ischemia-reperfusion, neutrophils are known to promote hepatocyte injury because they are responsible for the initiation of a sterile inflammatory response[178]. Neutrophil apoptosis constitutes an essential mechanism to attenuate inflammatory reactions and minimize tissue damage. Altered neutrophil apoptosis has been proposed to play an important role in a variety of inflammatory diseases and may be a marker of disease severity[179]. Chen *et al*[180] examined an experimental liver ischemia-reperfusion model and observed that the PGI_2 analog OP-2507 inhibited neutrophil apoptosis compared with untreated animals. In addition, OP-2507 administration moderated leukocyte adhesion in postsinusoidal venules and improved flow velocity in those areas[180].

Activated neutrophils release various inflammatory mediators, resulting in the upregulation of adhesion molecules on the endothelium and the promotion of endothelial damage. Neutrophil elastase is a protease that is stored in azurophil granules and released following the activation of neutrophils by inflammatory stimuli[181]. Neutrophil elastase has been shown to inhibit endogenous PGI_2 production by inhibiting eNOS activity, thereby contributing to the development of hepatic ischemia-reperfusion injury[182,183]. The administration of neutrophil elastase inhibitors significantly improved hepatic tissue blood flow, as confirmed by increased hepatic levels of 6-keto-PGF1α, a stable metabolite of PGI_2[78,79].

Mitochondria play a vital role in cell homeostasis; thus, mitochondrial dysfunction is closely associated with many pathological conditions. PGI_2 analogs have been proposed to regulate the expression of several mitochondria-related proteins, such as mitochondrial cytochrome C oxidase II and IV, beclin1, LC3 II protein, and PINK1. A reduction in mitochondrial damage was observed in lung fibroblasts treated with treprostinil, another PGI_2 analog[184,185]. Indeed, a previous report indicated that the administration of a PGI_2 analog in combination with superoxide dismutase and catalase in an animal model of warm hepatic ischemia led to significant improvement in mitochondrial function and improved survival[186]. In support of these findings, Hou *et al*[30] described the beneficial role of treprostinil in liver injury during renal ischemia-reperfusion injury: It alleviated hepatic oxidative stress and lipid peroxidation, downregulated hepatic toll-like receptor 9 and inflammatory processes, and inhibited hepatocyte apoptosis. Moreover, in animals treated with treprostinil, hepatic ATP levels appeared to be restored due to the upregulation of ATP synthase. Finally, treprostinil preserved mitochondrial biogenesis, restored mRNA expression to baseline levels and improved hepatic mitochondrial dynamics[30].

As mentioned above, oxidative stress is one of the main mechanisms of hepatic ischemia-reperfusion injury. PGI_2 analogs, in addition to their potent vasodilative and inhibitory activities, have cytoprotective effects by decreasing oxidative stress[187]. Specifically, a recent study showed that treatment with the PGI_2 analog iloprost resulted in increased superoxide dismutase, catalase, and glutathione peroxidase activity, resulting in the inhibition of ROS generation and recovery of hepatic microcirculation after ischemia-reperfusion injury[188].

New data regarding the cytoprotective mechanisms of PGI_2 analogs have been published in the last decade. MAPK signaling pathways regulate several biological processes, including apoptosis, through various cellular mechanisms. Stress-activated JNK and p38 MAPK (p38) mRNA and protein expression are increased following hepatic ischemia-reperfusion injury as a reaction to ROS overproduction[189,190]. A recent study demonstrated that beraprost sodium preconditioning ameliorated hepatic ischemia-reperfusion injury by suppressing the JNK and p38 cascades in a dose-dependent manner[28]. Anti-inflammatory, antiapoptotic and antiautophagic effects have been suggested as underlying mechanisms, mainly *via* the downregulation of TNF-α and IL-1β production and altered expression of the Bax, Bcl-2, Caspase-3, Caspase-8, Caspase-9, LC3, Beclin-1, and P62 genes. Similarly, the anti-inflammatory effects of PGI_2 analogs were observed in an experimental liver transplantation model. Specifically, animals treated with treprostinil before liver transplantation presented decreased hepatic tissue mRNA expression of ICAM-1, thereby reducing neutrophil accumulation. The mRNA levels of TNF-α, IL-6 and IFN-γ were decreased in the treprostinil group, whereas the mRNA expression of the anti-inflammatory cytokine IL-10 was increased[29]. Furthermore, the activity of cytochrome P450, an important indicator of allograft function, was significantly increased in animals treated with treprostinil in the early posttransplantation period[191].

The safety and efficacy of PGI_2 analogs have already been evaluated in liver transplant patients in clinical trials. Iloprost was administered by continuous intravenous infusion for 7 days after liver transplantation, and graft function was evaluated[192]. Improvements in allograft function and synthetic activity were observed, particularly in the early postoperative period. The results of another prospective, pilot, single-center, open-label, nonrandomized, phase I/II study were published in 2020 and further supported the efficacy of intravenous treprostinil in liver transplant patients [193]. A small group of patients who underwent liver transplantation and received peri- and postoperative treprostinil showed improved graft function, reduced ICU and hospital stays, and restored hemodynamic stability. In addition, the use of epoprostenol in the preservation solution to improve flushing of the peribiliary vascular plexus and biliary mucosa minimizes postischemic injury to biliary ducts, improves liver function tests and protects biliary strictures[194,195]. The

Table 3 Summarizing the main characteristics of the studies before 2000 regarding effects of prostacyclin analogs on hepatic ischemia-reperfusion injury

Ref.	Prostacyclin analog	Dose	Intervention	Species	Study size	Outcome
Monden *et al* [152], 1982	PGI_2	100 μg	Liver preservation for orthotopic liver transplantation	Mongrel dogs	6	100% 48 hours survival
Sikujara *et al* [155], 1983	PGI_2	350 ng/kg/min *i.v*	75 min Hepatic ischemia	Wistar rats	31	67% one-week survival
Tanaka *et al* [186], 1990	aPGI_2	350 ng/kg/min for 60 min *i.v*	90 min Hepatic ischemia	Rats		No effect alone
Sanchez-Urdazpal *et al* [172], 1991	Iloprost	200 μl/L storage solution. 3 μg/kg/min bolus administration through the aortic patch	Liver graft preservation	Lewis rats	12	91% survival
Goto *et al*[154], 1992	OP-41483	500 ng/kg/min *i.v*	Liver transplantation	Wistar rats	7	86% one-week survival
Abe *et al*[176], 1993	OP-41483	400 ng/kg/min	40 min normothermic liver ischemia	Wistar rats	8	Improved microcirculation and increased effective hepatic blood flow
Kim *et al*[156], 1994	OP-2507	2 pg/kg/min for 30 min, intraportal infusion 200 μg/l	Liver donor pretreatment, graft preservation. Dissolution in preservation solution	Mongrel pigs	6	Improved 5-day survival
Kim *et al*[157], 1994	OP-2507	2 pg/kg/min for 30 min *via* mesenteric vein administration	1 hour complete hepatic vascular exclusion	Mongrel pigs	7	86% 5-day survival
Anthuber *et al* [170], 1996	Epoprostenol	50 μg/ml solution	Liver donor bolus pretreatment	Lewis rats	8	Improved perfusion of liver sinusoids, reduced leukocyte adherence, increased bile production
Klein *et al* [195], 1999	Epoprostenol	500 μg	Orthotopic liver transplantation	Human	57	Reduced ischemia-reperfusion injury

PGI_2: Prostacyclin.

main characteristics of the studies regarding the effects of PGI2 analogs on hepatic ischemia-reperfusion injury are summarized in Tables 3 and 4.

Although several experimental studies have investigated the effects of PGI_2 analogs on hepatic ischemia-reperfusion injury, clinical data remain limited. Practical challenges due to the short life of PGI_2 analogs and the need for continuous administration have improved with the development of stable analogs, but further optimization is needed. Furthermore, PGI_2 analogs may have limited accessibility to some populations because of the high cost of the treatment. In addition, the clinical application of PGI_2 analogs in high-risk populations, such as cirrhotic and immunocompromised patients, poses significant safety concerns, primarily because of the potent vasodilatory effects of these drugs, their impact on immune reactions, metabolic considerations and altered drug metabolism.

Given the abovementioned challenges associated with PGI_2 analogs, well-designed clinical trials are essential to determine their optimal role in the treatment of hepatic ischemia-reperfusion injury. Large randomized controlled trials could determine whether PGI_2 analogs offer a clinical benefit over existing therapies. Combination therapy trials may evaluate whether the coadministration of PGI_2 analogs with various vasoactive agents increases the therapeutic benefits while reducing adverse events. Safety studies may assess the long-term safety and tolerability of PGI_2 analogs and define safe dosing strategies in high-risk populations. Pharmacokinetic and delivery optimization studies will lead to the development of novel stable formulations of PGI_2 analogs to overcome practical difficulties in administration and improve cost-effectiveness.

CONCLUSION

Hepatic ischemia-reperfusion injury is an important complication of liver transplantation and other clinical conditions, such as hemorrhagic and septic shock, trauma surgery, Budd-Chiari syndrome and major hepatectomy. Depending on the duration and degree of tissue damage, hepatic ischemia-reperfusion injury may result in a wide range of clinical presentations, from mild liver dysfunction to multiple organ failure. Many factors and pathways are involved in the pathophysiology of liver damage, including anaerobic metabolism, ATP depletion, intracellular acidosis, intracellular

Table 4 Summarizing the main characteristics of the studies after 2000 regarding effects of prostacyclin analogs on hepatic ischemia-reperfusion injury

Ref.	Prostacyclin analog	Dose	Intervention	Species	Study size	Outcome
Neumann *et al* [171], 2000	Epoprostenol	4 ng/kg/min *i.v* for 7 days	Continuous infusion after liver transplantation	Human	15	Improvement of hepatic-splanchnic oxygenation
Chen *et al* [180], 2001	OP-2507	1 μg/kg/min, 0.1 μg/kg/min	Hepatic ischemia	Sprague-Dawley rats	24	Ameliorated ischemia-reperfusion of the liver
Zardi *et al* [174], 2006	Iloprost	2 ng/kg/min, 6 h/day for 5 days	Portal flow velocity evaluation	Human	15	Improved hepatic perfusion
Gedik *et al* [188], 2009	Iloprost	10 μg/kg	45 min hepatic ischemia followed by reperfusion	Sprague-Dawley rats	10	Hepatoprotective effects
Ghonem *et al* [191], 2012	Treprostinil	100 ng/kg/min	Donor and recipient treatment prior liver transplantation	Lewis rats	58	Ameliorated hepatic injury reduced cytokines expression and improved CYP450 activity
Deng *et al*[28], 2018	Beraprost sodium	50-100 μg/kg	Hepatic ischemia-reperfusion	Mice	36	Ameliorated hepatic IR injury by suppressing inflammation, apoptosis, and autophagy
Almazroo *et al* [193], 2022	Treprostinil	20 ng/mL of storage solution	Hepatic ischemia-reperfusion	Sprague-Dawley rats	8	Reduced liver injury

calcium overload, mitochondrial dysfunction, oxidative stress, the activation of Kupffer cells and neutrophils, platelet aggregation, NO production, and cytokine release. Overall, hepatic ischemia-reperfusion injury has adverse effects on morbidity and mortality rates; therefore, new options to reduce liver damage are needed. Prostacyclin analogs confer protective effects on ischemic livers, mainly by regulating hepatic microcirculation, inhibiting platelet aggregation and alleviating oxidative stress. Experimental and clinical applications of PGI_2 analogs have revealed their ability to manage hepatic ischemia-reperfusion injury. Nevertheless, controlled clinical trials are needed to determine the safety and effectiveness of PGI_2 analogs in routine clinical practice.

FOOTNOTES

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REVIEW

Manual small incision cataract surgery: An ergonomic solution to tackle cataract backlog and challenging situations

Prateek Nishant, Arshi Singh, Arvind K Morya, Md Afroz Alam, Sony Sinha

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Abstract

Cataract surgery is still the most common surgery performed worldwide. It has evolved tremendously in terms of incision, from 12 mm to 1.8 mm, in terms of capsulotomy from envelope type to automated capsulorhexis, and from rigid intraocular lens to foldable intraocular lenses. Manual small incision cataract surgery (MSICS) remains a valuable technique, particularly in rural and under-served areas, due to its cost-effectiveness and simplicity. Its low logistics and favorable outcomes are particularly useful for managing the cataract backlog in developing countries. This review highlights the history and evolution of MSICS, and the reasons for the advent and popularity of this technique, especially in developing countries. It reviews the various recent modifications of the technique, for example, from a superior incision approach to temporal incision to customized MSICS, 2 mm MSICS, and astigmatism-correcting MSICS. It provides an overview of its applicability in complicated scenarios (viz., small pupil, compromised cornea, pseudoexfoliation, subluxated cataract, *etc.*). It briefly reviews the clinical trials on MSICS and its comparison with phacoemulsification. Finally, the review emphasizes why every ophthalmic surgeon must know MSICS, its relevance in postgraduate teaching, and the role of MSICS simulators for the same. Overall, the review presents a comprehensive picture of the present status of this technique in the surgical armamentarium of ophthalmology.

Key Words: Manual small incision cataract surgery; Astigmatism; Cataract; Complication; Cost-benefit; Efficiency; Teaching

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Core Tip: Cataract surgery is the most common surgery performed worldwide. It has evolved tremendously in terms of incision, from 12 mm to 1.8 mm, in terms of capsulotomy from envelope type to automated capsulorhexis, and from rigid intraocular lens to foldable intraocular lenses. Manual small incision cataract surgery remains a valuable technique, particularly in rural and underserved areas, due to its cost-effectiveness and simplicity. Its low logistics and favorable outcomes are particularly useful for managing the cataract backlog in developing countries. This review provides a comprehensive picture of the current status of this technique in the surgical armamentarium of ophthalmology.

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INTRODUCTION

Cataracts are responsible for the greatest share of the global burden of blindness and moderate-severe visual impairment. Approximately 50% of all blind eyes in low- and middle- income countries and about 5% in the first world are affected by cataracts[1,2]. Age-standardized pooled prevalence of cataract is about 17.2%, with a large proportion of these eyes suffering from poor visual acuity for distance and often for near, poor contrast, glare, colored haloes, photophobia, and discomfort in daily activities, often leading to psychosocial distress and impaired quality of life[3-5].

Globally, the disability adjusted life years (DALYs) due to cataracts have increased from 3.5 million (1990) to 6.7 million (2019). The age-standardized DALY rates due to cataract have decreased from 93.17 (1990) to 82.94 (2019), with an overall younger population now affected by cataract and opting for cataract surgeries[6]. The effects are compounded by various additional risk factors, including particulate matter pollution, smoking, a rising incidence of impaired glucose tolerance, and a higher body mass index of the younger population[7]. These problems, when presented in resource-deficient settings such as the developing world, pose significant challenges for ophthalmic care providers to deliver cost-effective options for visual recovery from cataracts while preserving the standards of safety and sterilization[8]. In addition, younger patients have more visual demands, leading to expectations of rapid visual recovery with reduced dependence on spectacles after cataract surgery[9]. The impact of these demands both on costs and carbon footprint have prompted the exploration of economically and environmentally sustainable alternatives to phacoemulsification surgery ("phaco"), which is currently the most commonly performed surgery for the management of visually significant cataract [10,11].

WHAT IS MSICS

Manual small incision cataract surgery (MSICS) is an alternative to phaco, involving a shelved trapezoidal corneoscleral incision for cataract lens removal, followed by intraocular lens (IOL) implantation to correct intraoperative aphakia. First described in the era of traditional extra- and intra-capsular cataract surgeries which were performed through large limbal incisions, MSICS has evolved to become the preferred option for extraction of the cataractous lens as a whole while retaining the capsular bag[12]. Even with increasing rates of phaco, MSICS continues to be relevant even today, and is advancing by leaps and bounds due to tremendous innovations in this technique[13]. Phaco and MSICS are regarded as complementary to each other in the repertoire of the modern cataract surgeon[14,15]. Experienced surgeons achieve comparable refractive outcomes and complication rates in their phaco and MSICS procedures, while exploiting the several advantages of MSICS in providing safe surgery in difficult situations, even in resource-scarce settings[16,17].

WHY MSICS

MSICS, with its proven track record of economic and environmental sustainability, may well be the answer to the woes of the modern era. MSICS has evolved over the years to become a fast, sutureless, convenient, resource-efficient, and carbon-neutral surgical procedure[18,19]. Whereas it was traditionally propagated to have limited application, modern MSICS can accommodate all of the requirements of cataract surgery as a true refractive surgery, from customized astigmatism correction to induced multifocality by manipulation of corneal incision morphology, and even multifocal IOL implantation without the need for any machine[20,21]. Similar to phaco, MSICS also has the potential to be combined with other medical and surgical procedures as well as alternative medical therapies[22,23].

The academic importance given to MSICS in recent published literature is miniscule compared to that given to phaco [15]. This review highlights the history and evolution of MSICS, and the reasons for the advent and popularity of this technique, especially in developing countries. It reviews the various recent modifications of the technique, for example, from a superior incision approach to temporal incision to customized MSICS, 2 mm MSICS and astigmatism correcting MSICS. It provides an overview of the applicability of MSICS in complicated scenarios (viz. small pupil, compromised cornea, pseudoexfoliation, subluxated cataract, coloboma, *etc*)[24]. It briefly reviews the clinical trials on MSICS. Finally, this review emphasizes why every ophthalmic surgeon must know MSICS, its relevance in post-graduate teaching and the role of MSICS simulators for the same.

SEARCH METHODOLOGY

The aim of this review is to put forth a comprehensive picture of the present status of the MSICS technique in the surgical armamentarium of ophthalmology. The objectives include an iterative review and analysis of literature to bring out the historical aspects of MSICS as well as various modifications and improvements achieved by surgeons worldwide, and how they have impacted the practice and outcomes of the MSICS technique as placed in perspective to phaco and other cataract extraction procedures, especially in the developing world. To achieve this, PubMed, EMBASE, Scopus, MEDLINE, Cochrane and Google Scholar were searched with the terms as mentioned in Table 1. These broad criteria amounted to a total of 12684 articles retrieved.

After removing duplicates, and excluding articles regarding only the intracapsular and conventional extracapsular cataract extraction (ECCE), and phaco, and considering only the articles with full texts available in the English language, 1566 articles were found to pertain to MSICS. Five independent reviewers went through the abstracts and full texts of all the articles, and shortlisted 116 articles for their relevance and uniqueness based on reference citation analysis and level of evidence. PRISMA flow diagram of the methodology is shown in Figure 1.

HISTORY OF MSICS

Prerequisites for a successful MSICS include a cooperative patient, a skilled surgeon, adequate anesthesia, full mydriasis, good instrumentation, and sterile environmental conditions[25]. The techniques described classically involved a combination of these in an inflexible manner. However, with experience, many modifications were made and the technique today is quite different from what it was in the last century.

CLASSICAL MSICS TECHNIQUES

In the initial days, a retrobulbar block was employed for anesthetizing the eye prior to any intraocular intervention. A combination of lignocaine 2%, bupivacaine 0.5%, and hyaluronidase 1:1500 was classically used, and 2-3 mL of the solution was injected into the retrobulbar space, *i.e.* within the cone of the rectus muscles. Considering the disadvantages of a retrobulbar block, like prolonged anesthesia, risk of retrobulbar hematoma and optic nerve injury, it was almost completely replaced by the peribulbar block, with injections at the junction of the medial and middle thirds of the eyelid in the upper fornix nasally, and the junction of the middle and lateral thirds of the eyelid in the lower fornix temporally [26].

For dissection of the superior limbus, the eye needs to be turned from the primary to a partially infraducted position. This used to be achieved using a superior rectus bridle suture (Figure 2A) with a monofilament nylon, sterilized braided cotton or silk thread, mounted on an eyed or eyeless needle, looped posterior to the superior rectus muscle blindly, and fixed onto the drape using a clamp (Figure 2A). This is especially useful in deep set eyes with prominent superior orbital ridges. Complications at this stage included subconjunctival hemorrhage, muscle hematoma or inadvertent injury to the eyeball. An increased incidence of post-cataract surgery blepharoptosis has also been attributed to the superior rectus bridle suture[27].

In the classically described MSICS technique, a superior fornix-based conjunctival flap is raised ("peritomy", Figure 2B) and monopolar heat or bipolar electric cautery is applied to stop bleeding from the scleral bed[28]. The tunnel incision is made in the superior or superotemporal region. The sclerocorneal tunnel is a secure valvular incision that is well covered with the conjunctiva. It is a triplanar incision due to which the inner lip (shelf) becomes self-sealing[29]. Externally located on the mid-limbal line, it traverses the Schwalbe's line internally, thus avoiding damage to the trabecular meshwork which lies more posteriorly[12]. It is regarded as that component of the MSICS technique which requires the most dexterity on the part of the surgeon, and several variations have been described. It consists of the following three subcomponents.

The external mid-limbal scleral groove or incision reaches almost a half-scleral depth in order to begin the plane for the sclerocorneal tunnel[14,30]. A straight linear incision or a smile shaped incision was initially described. A straight line with backward cuts on either side (after Blumenthal), or a chevron incision was also described for the same, the latter having least astigmatic effect (Figure 3). These incisions are made to lie in a zone called the Koch's Funnel wherein they do not cause considerable astigmatism upon healing (Figure 2C)[31,32]. The incision length was described to be approximately 6-8mm for different grades of cataract, and to accommodate the rigid polymethylmethacrylate (PMMA) IOL with

Table 1 Search terms for the present review

Number	Search term
1	Manual small incision cataract surgery
2	Cataract surgery
3	Cataract extraction
4	Ocular anesthesia
5	Sclerocorneal tunnel
6	Capsulotomy
7	Hydrodissection
8	Hydroprolapse
9	Nuclear rotation
10	Viscoelastic substances
11	Viscoexpression
12	Snare
13	Nucleofractis
14	Nuclear bisection
15	Trisection
16	Cortex
17	Hydroimplantation
18	Irrigation
19	Aspiration
20	Posterior capsule rupture
21	Vitreous loss
22	Endophthalmitis

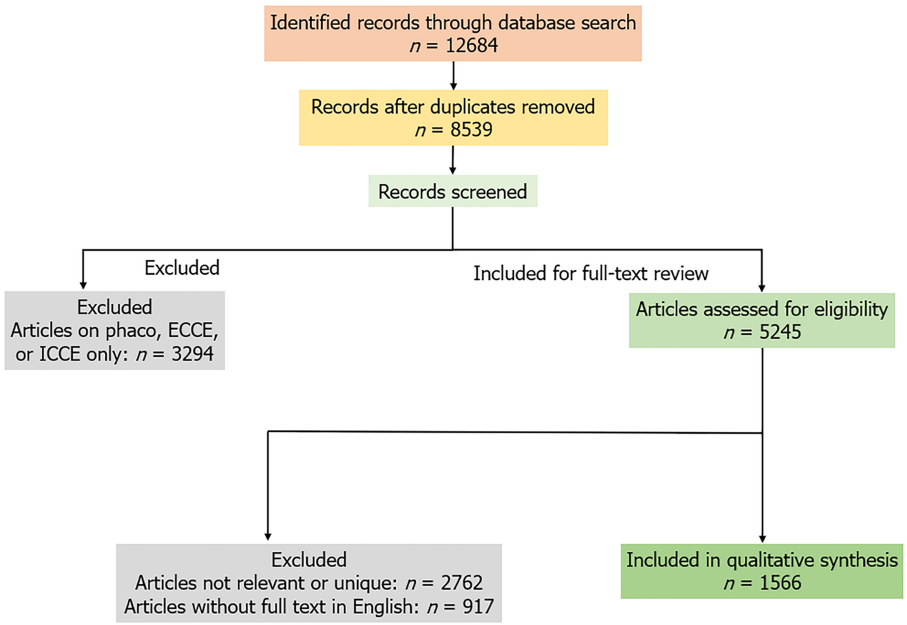


Figure 1 PRISMA of the methodology. ECCE: Extracapsular cataract extraction; ICCE: Intracapsular cataract extraction.

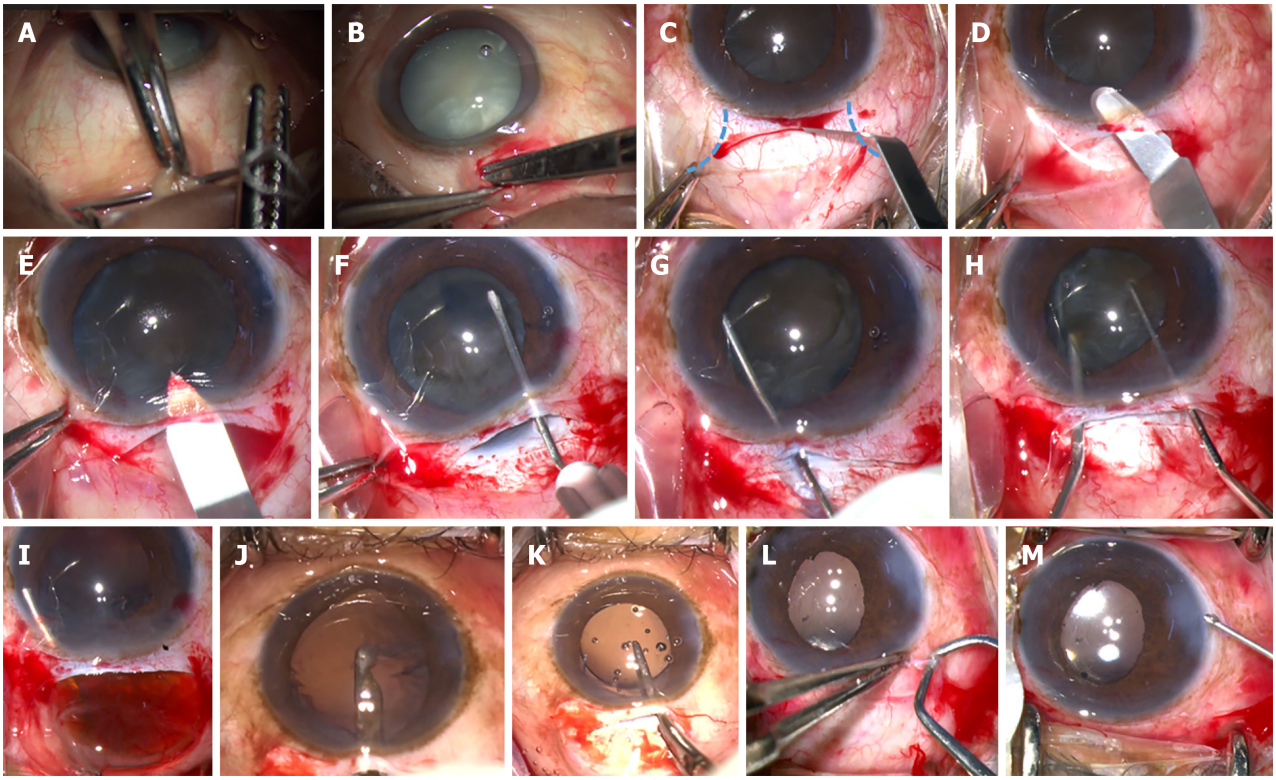


Figure 2 Steps of manual small incision cataract surgery. A: Superior rectus bridle suture; B: Superior conjunctival peritomy; C: Scleral groove (dashed lines estimate the extent of Koch's Funnel); D: Sclerocorneal tunnel dissection; E: Keratome entry; F: Continuous curvilinear capsulorhexis; G: Hydrodissection; H: Nuclear rotation and prolapse; I: Nuclear delivery by viscoexpression; J: Irrigation and aspiration by simcoe cannula; K: Intraocular lens implantation; L: Cautery to repose the conjunctiva; M: Sideport hydration.

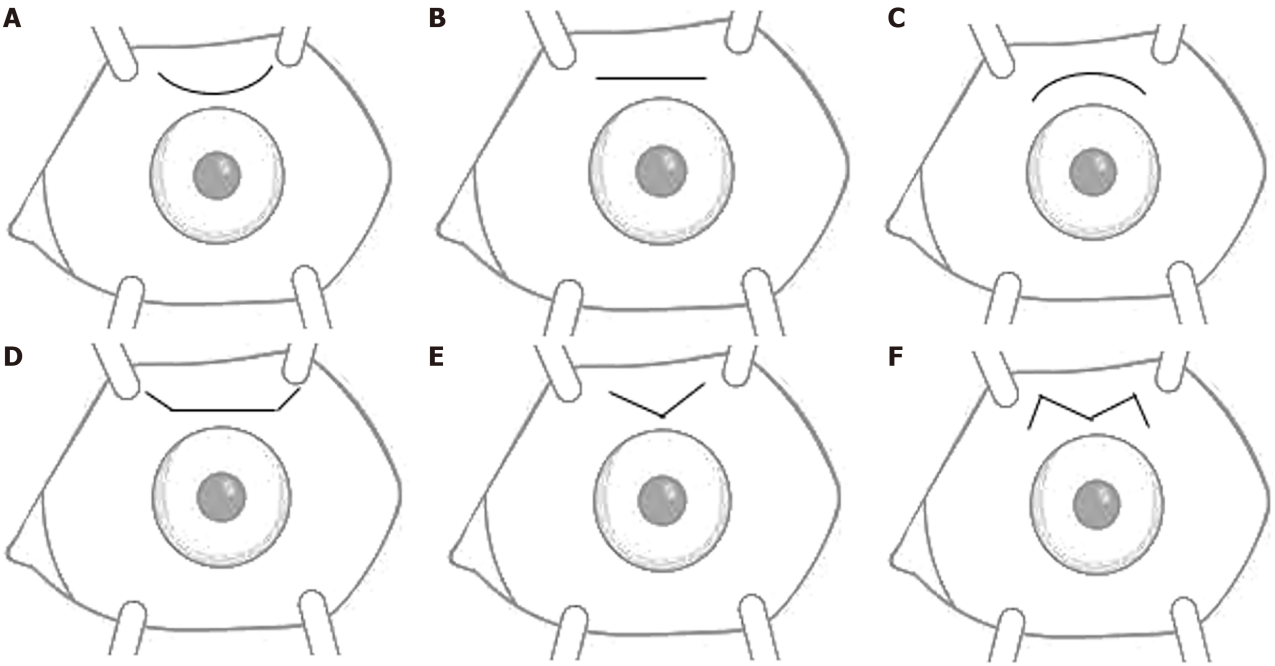


Figure 3 Various incision designs in manual small incision cataract surgery. A: Frown; B: Straight; C: Smile; D: Straight with Blumenthal back cuts; E: Chevron; F: W-shaped or M-shaped incision for manual small incision cataract surgery with trabeculectomy.

optic diameter of approximately 6 mm.

The sclerocorneal dissection is carried out parallel to the plane of the sclerocornea, at one-third to half-depth to create a 1-1.25 mm dissection in the sclera and a similar tunnel width in the clear cornea to achieve a valvular nature (Figure 2D). A crescent knife is classically described to be used for this purpose, cutting while coming outward, tilting the blade on either side of the lateral tunnel by 45 degrees to follow the contour of the globe. The dissection is advanced 1-1.25 mm into the corneosclera on both sides to form a funnel like configuration with side pockets[30]. This yields an external wound size of 6-8 mm but internal (corneal) entry wound about 2.5 mm larger to accommodate the full width of the nucleus[29,33,34].

The internal entry wound is made using a keratome (Figure 2E). The entry is initially made centrally with the sharp keratome tip pointing downwards to prevent Descemet's membrane detachment. Then the entry is extended on either side, cutting while going inward to maintain the plane, the entire internal entry being approximately parallel to the limbus, thereby forming an overall trapezoidal section[29,34].

A 15-number Bard-Parker blade is classically used for the scleral incision, but a crescent knife, keratome or hockey-stick knife may also be used. In the earliest adaptation of the technique in resource-poor settings in India, a piece of sterilized shaving blade would be held firmly with forceps and broken using a blade-breaker, then bent and held in a blade-holder to be used for tunnel construction.

Anterior capsulotomy removes the central part of the anterior capsule, which is the barrier to access the lens material from the anterior chamber (AC). For this purpose, a side-port is made and the anterior capsule is stained with trypan blue dye under an intracameral air bubble. While a good capsular staining helps in good visualization of the same during intraocular procedures, the dye also changes the texture and fragility of the anterior capsule, making the capsulotomy more controlled. It can be performed before or after the opening of the internal entry wound.

Capsulotomy is traditionally performed under cover of a viscoelastic substance like 2% hydroxypropylmethyl cellulose, which maintains the AC, tamponades the anterior capsule and prevents uncontrolled fluttering or runaway of the capsular flaps and tags. Earlier reports showed the success of an envelope technique wherein approximately U- or V-shaped cuts on the anterior capsule were fashioned like the flap of an envelope, which gave sufficient access to extract the lens matter and implant the IOL, but showed complications like postoperative dyscoria, IOL tilt, and decentration. Can-opener capsulotomy was thus resorted to. An approximately circular opening with ragged edges is fashioned using a cystitome, but it could be performed in various shapes depending upon the preference of the surgeon (Figure 4). While suitable for most MSICS cases, it often results in several capsular tags which are at risk of runoff to the periphery if the AC is not maintained. Thus, can opener capsulotomy may be risky in the hands of beginners. The manual continuous curvilinear capsulorhexis is thus the preferred technique for anterior capsulotomy (Figure 2F). An adequately sized capsulorhexis is warranted, centered on the visual axis for optimum outcomes. Studies have found altered effective lens position in inadequately sized capsulotomies, dysphotopsias and compromised retinal images in decentered capsulotomies, and posterior capsule wrinkling and opacification (PCO) in large capsulotomies[35].

Hydrodissection is performed using a Rycroft cannula, injecting small aliquots of fluid below the anterior capsular rim, thereby causing anteroposterior waves of fluid free the cortico-capsular adhesions (Figure 2G). In dense nuclei, this may not be required as the cortical adhesions are flimsy, and are dissected easily on nuclear manipulation. With the combination of an adequate amount of fluid and an adequately sized anterior capsulotomy relative to the size of the nucleus, the nuclear mass can easily be prolapsed into the AC by this maneuver alone ("hydroprolapse"). In other cases, the nucleus can be "wheeled out" by lifting one pole with one or two blunt instruments such as Sinskey hooks, ball point manipulators or cannulas, and progressively rotating the nucleus while lifting anteriorly like a tire changer's rolling tire technique (Figure 2H)[36]. In the earliest techniques, this step was often omitted if a can-opener capsulotomy was performed in selected cases, the nucleus being directly lifted in the AC by a Sinskey hook[37].

The AC is filled with viscoelastic substance to raise the intracameral pressure, push down the posterior capsule and coat the corneal endothelium. A dispersive viscoelastic like hydroxypropyl methylcellulose is most suitable for the purpose. Nuclear delivery is achieved in toto through the sclerocorneal tunnel, aided by viscoelastic pressure (Figure 2I), blunt irrigating instruments such as a cannula or vectis. A serrated wire vectis may also be equally effective. Early trends for smaller incisions in MSICS were matched with increasing adoption of nuclear fragmentation techniques. Nuclear bisection and trisection were described in the tunnel whereby remaining nuclear fragments were oriented with the long axis in the median of the tunnel length, allowing easy extraction using hydro- or viscoexpression or a vectis, aided by pressure on the posterior lip of the incision. Nuclear division inside the AC ("manual phacofragmentation") had been described by Kelman in 1967 using Ringer forceps, and was further promoted by Kansas. Suture loops were described to bisect and trisect the nucleus in the AC-the early works of Keener and Shah made popular the snare-assisted technique for nucleofractis[38]. Other techniques included nucleosuction with a modified Simcoe cannula, phacosandwich technique (capturing the lens mass between a sinskey hook above and a vectis below), and various nuclear debulking techniques. The nuclear fragments are then removed in the usual manner.

Nuclear matter removal under fluid pressure has also been very popular. Various irrigating cannulas were described for pushing balanced salt solution (BSS) into the AC, thereby expressing the nucleus out[39]. Blumenthal introduced the use of AC maintainer (ACM) in his technique of MSICS for continuously maintaining the AC using gravity-fed fluid and aided nucleus delivery by pushing it out once the incision was held open by a sheet glide inserted beneath the nucleus and its outer end tapped[40]. ACM is a hollow sterile surgical steel tube (0.9 mm outer diameter and 0.65 mm inner diameter) inserted at one of the side ports, preferably on the temporal side. The steel tube is attached by a sterile pipe to a BSS bottle suspended 50-60 cm above eye level[41]. It is also possible to do manual phacofragmentation even under Blumenthal's technique with ACM.

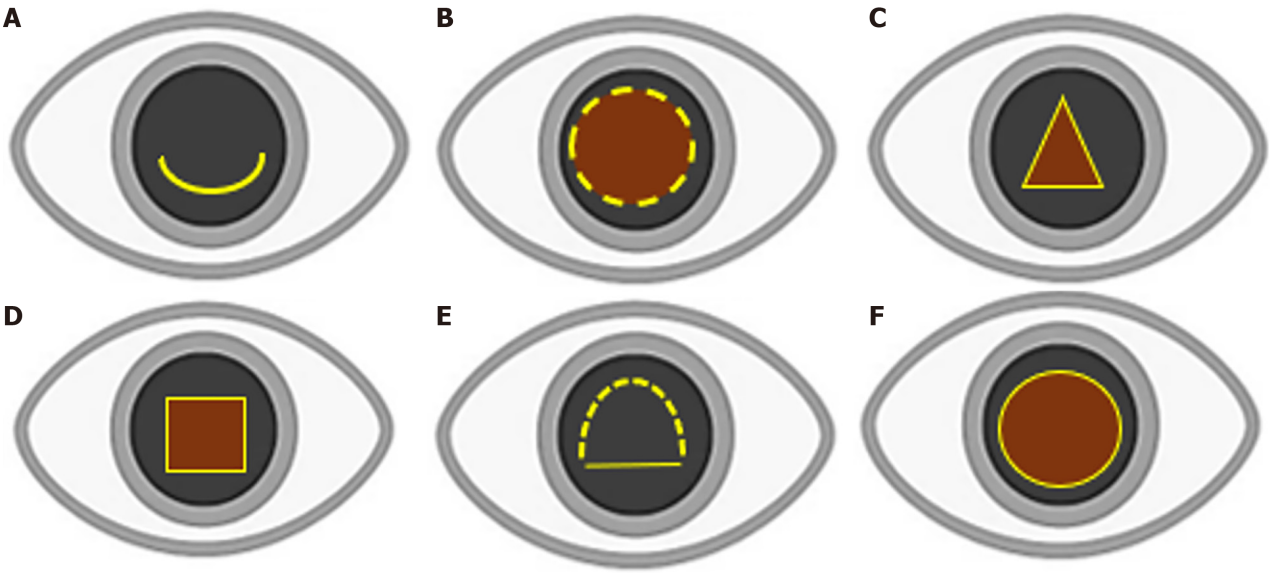


Figure 4 Various techniques and shapes of anterior capsulotomy in manual small incision cataract surgery. A: Envelop, B: Can opener; C: Christmas tree; D: Square; E: D-shaped; F: Continuous curvilinear capsulorhexis (preferred).

An irrigation-aspiration Simcoe cannula is used to clear the cortex, with a sterilized glass bottle containing BSS providing gravity-fed irrigation, and a 5 mL syringe connected to the aspiration channel (Figure 2J). If the ACM is used, irrigation need not be connected to the cannula, and a single port aspiration cannula may be used. Implantation of a rigid, monofocal PMMA IOL in the capsular bag completes the procedure (Figure 2K) followed by removal of the viscoelastic substance, optional closure of the conjunctiva by electrocautery (Figure 2L) and hydration of the side-port (Figure 2M). The self-sealing incision usually requires no sutures, but application of one or two sutures, if needed, may reduce the astigmatic effect of the incision.

EVOLUTION OF TECHNIQUES

Modern MSICS is fast, efficient and safe-only a few minutes in duration in the hands of experienced surgeons (Video). There have been several modifications and innovations described for each step of the procedure, that altered the complete scenario of cataract surgery making MSICS truly a surgical technique of the future[42].

Anesthesia

Prolonged anesthesia and full akinesia of the eye to be operated are no longer required. In the preoperative area, proparacaine (0.5%) is instilled once and supplemented with lignocaine jelly (2%) after a while. No sedation is employed. Constant surgeon–patient communication is maintained, allaying the patient's apprehensions. A small piece of sterile gauze soaked in lignocaine may be applied to the area before scleral dissection. If the patient complains of pain, then 0.75 mL of 2% lignocaine is infused into the subtenon space using a blunt cannula[43]. Supplementation can be given at any stage of surgery if required. Intracameral 0.5 mL preservative-free lignocaine is irrigated into the AC[43]. Some cooperative patients are able to tolerate the procedure in topical anesthesia, while for some uncooperative ones, a peribulbar block is still used[44]. General anesthesia is still required for patients with psychological infirmities. Levobupivacaine and ropivacaine are other drugs recently introduced for infiltration, mainly for subtenon and peribulbar anesthesia.

Pupil dilation

While a full pupillary dilation is still ideal for all MSICS procedures, the advent of intracameral mydriatic pharmacologic agents as well as pupil dilation devices and speculums have diminished the mandate for prior pupillary dilation. For intracameral use, a commercially available combination of tropicamide, phenylephrine and lignocaine is commonly used [45]. Pupil dilation devices such as the B-Hex ring have been successfully used in various cases with small and rigid pupils[46].

No bridle suture

The superior rectus bridle suture has been done away with. Infraduction of the eye is now achieved by fixation of the eyeball using a forceps in the non-dominant hand. Sometimes, a partial-thickness posterior scleral groove is made posterior to the sclerocorneal tunnel to aid the grip of the forceps and prevent slippage of the fixation point. MSICS by a temporal approach does not require a rectus suture at all due to adequate exposure, avoiding the brow or nasal prominences. It is thus the preferred technique in deep set eyes[47].

Peritomy

Conjunctival peritomy is also not done by many surgeons who find it faster to approach the sclera transconjunctivally. In addition, the incision and tunnel are increasingly being made without the use of cautery on the scleral vessels, because the cells, growth factors, nutrients, and cytokines in the blood result in a theoretically more natural healing response.

Sclerocorneal tunnel

The frown incision for MSICS was described by Singer and is the most popular technique today[48]. It results in an approximately trapezoidal tunnel with side-pockets to accommodate large lens masses. Modifications of the incision are shown in Figure 3. For beginners, novel stamps have been developed to aid the visualization of the approximate limits of the incision or trapezoid to make a consistent tunnel[49,50]. Larger and wider tunnels have been described. For example, the extra-large temporal tunnel cataract extraction procedure consists of a 8-10 mm large modified MSICS sclerocorneal tunnel 4.5-5 mm from the limbus[51]. A combination of two adjoining frown-shaped incisions, a combined large sclerocorneal tunnel and an almost 6-clock hour internal keratome entry has been used in Mohanta's double SICS technique, also called the large incision cataract surgery technique. After nuclear removal, the tunnels are apposed with only three 10-0 monofilament nylon sutures – one at the vertex of the two frown incisions, and one at the center of each tunnel. This allows an internal opening to accommodate the largest of lens masses, thereby making the technique effective to manage the most challenging nuclei of cataracta brunescens and nigra.

The sclerocorneal tunnel is now customized according to astigmatism of the patient, and a mix of factors are considered while predicting the astigmatic effect thus obtained - the incision location, size and shape, configuration of the tunnel, pre-existing ocular pathology, and whether sutures are used[30]. The term surgically-induced astigmatism (SIA) has now been transformed to surgically corrected astigmatism by custom designing of the incision according to the pre-existing corneal astigmatism (total keratometry) as measured on optical biometers, and intraoperative estimation of corneal distortion by keratometric software analyzing the shape of a ring projected onto the cornea[14,52]. The frown incision has been exaggerated to an inverted U-shape to enhance the delivery of nuclei through incisions of 2 mm chord length, combined with a phacofracture technique[42,53].

MSICS can be done through a 6 mm curvilinear clear corneal tunnel, but it was found that SIA is significantly higher in clear corneal MSICS than in sclero-corneal[33]. The astigmatic effect is far lesser when a postlimbal 2.2 mm or 2.8 mm keratome entry is used to make a small initial tunnel and enter the AC in one go, the entry later extended using a blunt 5.5mm keratome ("enlarger blade"). Good results in multifocal IOL implantation can also be achieved with the correct estimation of the surgically corrected astigmatism and efficient surgical technique[42]. A temporal approach to neutralize a steeper corneal curvature in the horizontal meridian (commonly seen in elderly patients) preserves the superior conjunctiva for future glaucoma filtration surgeries. In addition, it induces lesser astigmatism compared to a superior incision due to orientation of scleral fibers and more distance from center of the cornea[29].

Combination of MSICS with trabeculectomy entailed the innovation of a M or W-shaped incision (after Khurana *et al* [54]) or a Flying Eagle incision (after Malik *et al*[22]). The posterior extensions of the M/W or the flying eagle configuration allow the placement of sutures akin to standard trabeculectomy flaps, while the rest of the triplanar tunnels seal on their own like standard MSICS tunnels.

The paracentesis

The paracentesis can be created using a side port knife, lance tip (15 degree) knife, microvitreoretinal knife, partial entry of the keratome, and even a simple 21G needle puncture of the limbus. An initial small internal keratome entry in the sclerocorneal tunnel helps to maintain the AC while allowing a port to perform intracameral maneuvers like air bubble injection, anterior capsular staining, viscoelastic injection and anterior capsulotomy. This entry can later be enlarged to the full width of the tunnel. This has nearly eliminated the need for a separate paracentesis.

Anterior capsule

Maintaining the AC leads to better postoperative outcomes due to lesser mechanical stress on the cornea as well as preservation of corneal endothelial function[55]. Thus, various viscoelastic substances have been used in MSICS. Continuous viscoelastic infusion through an ACM has also been described[56]. Tunnel floor entry has been described to lessen the amount of fluid or viscoelastic loss through the large tunnel[42]. It has been found that ACM can help completely avoid the use of viscoelastic during surgery, which can be an effective technique for MSICS, or MSICS with trabeculectomy[57]. Thus, anterior capsulotomy can be performed under viscoelastic or under fluid. Manual techniques of anterior capsulorhexis remain essentially the same, except that for a continuous curvilinear capsulorhexis, a novel technique involves the use of an aspiration cannula to engage the leading edge of the capsular flap (Can-Vac technique) [58]. There are no contraindications to the use of modern automated techniques of anterior capsulotomy, utilizing femtosecond laser, CAPSUlaser® (Excel-Lens inc., CA, USA), precision pulse capsulotomy technique, plasma blade *etc.* but they are neither required, nor cost effective in most settings.

Nuclear management

Nuclear rotation and prolapse in the AC using two instruments has been found to cause lesser stress on the zonules. This bimanual technique utilizes any combination of Sinskey hook, Kuglen hook, iris repositor, cyclodialysis spatula, ball-point manipulator and even phaco choppers of various designs, that are effective in the hands of skilled surgeons. Nuclear rotation in MSICS is safe even in posterior polar cataracts if the fluid dynamics are correctly understood[59]. Attempts for nuclear fragmentation into the smallest possible dimensions have paralleled the reducing size of the MSICS incision. Recently, nucleofractis in the AC has been made very popular by revival of the snare technique. The double

nylon loop snare and Shah's snare have been recently reintroduced and popularized[38,60]. Boramani *et al*[61] described an axe-shaped chopper wherein the dominant hand uses this instrument through the side port moving tangentially across, to an iris repositor which through the main port supports the prolapsed nucleus from behind.

Prechoppers can chop the nuclear mass in the bag, making it convenient to prolapse out and remove each piece sequentially. Bhatti utilized the Akahoshi prechop technique for in-the-bag nuclear fracture[62]. Various other forward-cutting prechoppers (Jacobovitz prechopper, Sohel Khan prechopper, Mohanta's prechopper) have been utilized for in-the-bag nuclear fracture. The Mi-Loop, another modern in-the-bag nuclear fracturing device, may also be used for the purpose, but is expensive. Endoexpression of the nuclear material in whole or part has been described by Boramani *et al* [63], wherein the nuclear mass is mechanically pushed from its lower pole by a blunt instrument introduced through a paracentesis. Nuclear extraction has also been achieved by fluid pressure using modifications of irrigating cannulas and irrigating vectis. Various combinations of viscoexpression, endoexpression, phacosandwich and fishhook techniques are also in vogue[63-65].

Cortical aspiration

Simcoe, reverse simcoe, J-simcoe, and single port aspiration cannulas, with or without sandblasted tips, are all being used by various surgeons for cortical cleanup and polishing today. Another recent innovation in cortex aspiration is the use of a spring-assisted syringe for controlled aspiration pressure in order to make the procedure more predictable[66]. A fluid jet applied onto the posterior capsule removes fine adherent cortical fibers, while stubborn lens epithelial cells on the anterior capsular rim can be removed using a ring-shaped or olive-tipped capsule polisher.

IOL implantation

Modern day foldable IOL implantation is possible through the sclerocorneal tunnel of MSICS using a direct introduction using non-toothed forceps, or using the injector system similar to phacoemulsification depending upon the size of the tunnel incision. Some surgeons use the injector unaltered even through a larger incision, while some others prefer to slit the tip of the injector to lessen the stress on the IOL. Irrigation and aspiration of viscoelastic, followed by a final lavage of the AC after IOL implantation removes any remainder of viscoelastic. Hydroimplantation of the IOL using a continuous ACM infusion is also popular. Retained viscoelastic can raise intraocular pressure (IOP) postoperatively, and the latter technique completely avoids the need for viscoelastic removal, utilizing only fluid to form the AC while implanting and dialing the IOL. Even toric, presbyopia-correcting and advanced technology IOLs can be easily implanted using this technique.

Wound closure and patching

Intraoperative antibiotic prophylaxis against endophthalmitis is the recent trend, with intracameral moxifloxacin injection showing the best evidence towards prevention of this vision-threatening complication after MSICS[67]. A recent study has also shown addition of Amikacin in the BSS irrigating fluid to be beneficial in preventing endophthalmitis[68]. A recent innovation after hydration of the sideport is the Siep's test - a novel test to check the wound integrity while forming the AC after completion of the IOL implantation procedure. It is the application of 2-3 drops of 5% povidone iodine to identify wound leaks, with the dual purpose of further sterilizing the ocular surface[69]. In modern MSICS, following the final hydration of the wounds, the eye may or may not be patched depending upon the surgeon's preference and patient's eyelid and ocular movements. If the postoperative status is satisfactory, the patient is provided a pair of clear polycarbonate protective goggles to wear, and discharged.

COMPLICATIONS OF MSICS

The profile of complications encountered in MSICS are similar to that of phaco and other cataract extraction procedures. Complications related to anesthesia include the adverse effects of anesthetic drugs as well as the technique of administration of the agents, with no significant differences observed in subtenon and peribulbar block techniques[70]. Some of the complications are similar to any other intraocular surgery, while others are unique to the MSICS procedure itself.

Intraoperative complications include bleeding, improper incision architecture leading to full thickness scleral penetration with uveal show, or too superficial a plane of scleral dissection leading to poor sealing of the incision[71]. The sclerocorneal tunnel may be too short leading to a premature entry or too long leading to high SIA. It may be jagged, multiplanar or irregular, leading to leaking and intraoperative shallowing of AC as well as postoperative hypotony[72]. Descemet's membrane detachment at the incision sites is another complication, necessitating intraoperative or postoperative air or gas tamponade[73]. Intraoperative damage to the corneal endothelium or iris may occur due to various causes. The capsulorhexis may be inadequate or improperly shaped, leading to difficulties in handling of the nucleus. It may run off to the periphery or even trans-equatorially, thereby causing a posterior capsular rupture (PCR). A large PCR may lead to the whole nucleus unexpectedly dropping into the vitreous cavity, although it is infrequent in MSICS. A PCR may disrupt the vitreous face, leading to vitreous prolapse through it into the AC and out of the large MSICS wound, wherein meticulous limited anterior vitrectomy would be warranted. IOL may be implanted in the bag if the PCR is small, or in the ciliary sulcus if the latter is clearly visible. If there is doubt, the patient may be left aphakic. Larger anterior capsulotomies performed for harder nuclei may limit the ability to implant a standard PMMA IOL, in which case a PMMA IOL with a 6.5 mm optic may be preferred. There is risk of IOL decentration, given that the PMMA IOLs are 12.5 mm in size and the ciliary sulcus may be larger especially in myopes. A reverse optic capture may help in long-term centration of the IOL, however, there is limited evidence in its favor in MSICS procedures. Postoperatively,

complications such as striate keratopathy, choroidal detachment, endophthalmitis, and hyphema may be encountered due to various causes, all of which are insufficiently discussed in literature as being attributable to the MSICS procedure per se[74]. However, the incidence of major complications is seen to be lesser in phaco than MSICS, making phaco an overall preferred choice of surgery today.

Postoperative corneal edema and AC inflammation usually resolve with medication and do not require additional procedures. However, surgical management of major complications after MSICS is challenging because of the resource constraints due to which the MSICS was performed in the first place. Many centers performing MSICS are not equipped with advanced operating microscopes, automated vitrectomy systems, or intraoperative visualization aids like endoilluminators or microscope-integrated optical coherence tomography systems. As usual, the surgeon's discretion in the setting of a complication is the most important factor in determining the final outcome in these cases. With proper precautions and safe technique, MSICS results in early visual rehabilitation, return to work and restoration of quality of life similar to phaco.

MSICS IN SPECIAL SITUATIONS

Cataract subluxation

Subluxated cataract warrants special considerations, including the need for careful assessment and preservation of remaining zonular support, the possibility of trans-zonular vitreous in the AC, potentially difficult capsulorrhexis and nuclear prolapse as well as the risk of losing the bag. Goel *et al*[24] showed that in cases of subluxations less than 90°, MSICS can be easily done. But beyond this degree and in larger subluxations, a larger capsulorhexis is required which may be difficult to achieve with a larger incision. Manipulation during the prolapse of nucleus may lead to further zonular dialysis. There are rare conditions like lens coloboma associated with subluxation in which rotation of nucleus and prolapse is quite difficult. In these scenarios, the preferred choice is phacoemulsification. In a study, more than 76% of the MSICS eyes were successfully implanted with posterior chamber IOL along with the retention of capsular bag with subluxation. The modified Bluementhal technique is found to be effective in such subluxations of various degrees[75].

Phacomorphic glaucoma

MSICS is the preferred choice in phacomorphic glaucoma as per studies by Rajkumari *et al*[76] and Ramakrishanan *et al*[77] and has shown better results when post-operative visual acuity, intra-operative and post-operative safety were assessed. MSICS should be preferred due to preexisting short AC depth, large hard nucleus, zonular weakness and compromised cornea.

Pseudoexfoliation syndrome

In a study by Desinayak *et al*[78], MSICS was found to be a beneficial and convenient surgical technique for the patients of pseudoexfoliation syndrome and secondary glaucomas associated with it due to various co-existing morbidities like hazy cornea, poorly dilated pupil, low endothelial cell count and increased chances of zonular dialysis[78]. Proper precautions must be taken for anticipated difficulties during the surgery.

Intumescent white cataracts

There are three different vector forces coming into action in white intumescent cataracts, thereby making capsulorhexis the most exigent step during surgery. There are higher chances of Argentinian Flag Sign which may further leads to posterior capsular rupture and nucleus drop[79]. If a successful capsulorhexis is achieved, both MSICS and phacoemulsification can be performed, but in case of any extension it is safer to carry out MSICS to achieve better visual outcomes free of any complications[34].

Compromised corneas with low endothelial cell density

Mechanical distortion of the cornea, fluid turbulence in the AC, direct trauma by intraocular instruments, nuclear fragments, or IOLs, and reactive oxygen species, all have been implicated in causing corneal damage during cataract surgery, and these are theoretically more common in MSICS than phaco[80]. However, the study by Gajraj *et al*[81] and Kusumesh *et al*[82] had clearly shown that MSICS with posterior chamber IOL implantation is the only choice in compromised corneas with low endothelial cell count to provide the best possible functional vision. The authors were able to achieve good visual outcomes in such patients by doing MSICS[81,82]. The MSICS procedure causes endothelial cell depletion of approximately 16%, which is similar to other modalities of cataract surgery[80].

MSICS and premium IOL implantation

With the advent of the Boramani Nomogram for surgically corrected astigmatism, customized MSICS, smart small incision cataract surgery (SICS), and 2-mm incision Sahu's MSICS, surgeons can implant all types of premium IOLs without any hesitation as the post-operative refractive surprises are reduced to bare minimum with excellent quality of vision. The success of these advanced techniques also proves that MSICS is no more the surgery of choice for the underprivileged but for the premium segment, too[14].

MSICS IN DEVELOPING COUNTRIES

MSICS is largely practiced in developing nations whereas phacoemulsification with its various technology-driven and commercially driven refinements is a more popular cataract surgery in the west[15]. MSICS is a boon and a logical solution for countries with limited resources with higher cataract morbidity. Multiple studies have suggested similar safety and efficacy for the two procedures with MSICS being more cost-effective with lesser surgical time[83,84]. As stated previously, it also scores over phacoemulsification in being more environment friendly with a smaller carbon footprint[19].

Burden of cataract in developing (middle- and low-income) countries

Cataract blindness continues to be one of the greatest public health challenges, with World Health Organization reporting it to be the main cause of preventable blindness[85,86]. A global study conducted in 2020 stated that 39.6% of overall 43.3 million blind (17.0 million) and 28.3% of 295 million with moderate or severe visual impairment (83.5 million) suffered from cataract as the cause of visual impairment[87]. Over the last three decades, the number of DALYs due to cataracts increased by 91.2% making it the second largest burden of eye disease[7]. Risk factors associated with higher cataract burden were female sex, aging, lower socio-economic status among others. The age-standardized DALYs of cataracts due to risk factors were highest in areas having low to middle sociodemographic indices. The prevalence of cataract-related blindness was higher than the global average only in nations of South Asia (62.9%) and Southeast Asia and Oceania (47.9%)[87].

In Asia, cataract is the most common cause of blindness and vision impairment followed by refractive error and near vision impairment in terms of the burden of DALYs[88]. India contributes almost 12 million of the total 22 million blind people worldwide. Of these, cataract has been reported to account for 50%-80% of the bilaterally blind (vision < 20/200 in the better eye). The incidence of cataract is 3.8 million/year with a backlog of approximately 6 million/year in India[89]. The high cataract burden in developing nations like India necessitates that a fast, economical yet effective cataract surgery like MSICS ought to be a well-utilized resource in the hands of many ophthalmic surgeons. High volume cataract surgery in resource-scarce settings can be accomplished by the majority of patients undergoing MSICS[90]. The overall complication rate is similar for MSICS and phaco. However, it has been shown that trainee surgeons have significantly more complications with phaco than with MSICS[91]. MSICS procedures have been shown to have short learning curves, thus, institutions training early-career surgeons must have MSICS as one of the preferred surgeries for their patients[92].

Cost considerations of phacoemulsification vs MSICS

In developing nations, phaco with the requirement of a permanent and reliable source of electricity, costly machinery needing regular maintenance and machine-specific consumables, may face limited use in resource-challenged situations. Also, safety may be compromised in extremely dense cataracts and compromised corneas, commonly encountered in patients of developing nations with delayed health-seeking behavior[18]. A study of the provider's direct total annual costs using a "micro-costing approach" showed that phaco had higher direct costs (25.55 dollars) compared to MSICS (17.03 dollars) due to the cost of additional equipment and materials required in phaco. Also, a combined total of the costs incurred by the patient were studied and were found to be similar for MSICS and phaco (12.37 dollars)[93]. Another study comparing cost of cataract surgeries performed by residents found a higher total cost for phaco (416 dollars), *vs* ECCE (284 dollars)[94]. In a comparative study in India, phaco costed 42.10 dollars, whereas MSICS costed only 15.34 dollars. It was estimated that 10.65 dollars was the fixed-facility cost common to both MSICS and phaco[95]. Similar studies conducted in Nepal and Thailand have also demonstrated lower direct costs of MSICS compared to phaco (15-62.25 dollars for MSICS to 70-104.15 dollars for phaco)[96]. The use of locally manufactured viscoelastic devices, IOLs and pharmaceuticals dramatically lowers costs, with some surgeons reusing some consumables to further bring down the cost of the procedure[94].

A systematic survey showed that the cost utility analysis for MSICS shows savings of 79.57 dollars per unit gain in LogMAR best-corrected visual acuity, and 8.91 dollars per QALY gained in India with better incremental cost-effectiveness ratio *vs* phaco[96]. According to a study by Jongsareejit *et al*[97], cost-effectiveness ratio for MSICS was 13215.50 dollars compared to phaco which was 17561.70 dollars[97]. Improvement of QALY values - a surrogate marker for cost-benefit analysis - is better in treatments providing early rehabilitation like phaco traditionally. However 3-month data showed no statistical difference in visual gain or complication rate between phaco and MSICS[98]. Also, incision-related modifications in MSICS reduce spectacle dependence by inducing mild myopic astigmatic errors which may be very useful in resource-constrained environments. Thus, the cost-utility difference may be significantly better for MSICS compared to phaco[95,97].

A short turnover time for MSICS with a minimal cost per case makes it a prime candidate for high-volume surgery[90]. Hence, MSICS scores over other existing alternatives of cataract extraction from cost-effectiveness and cost-minimization approaches[94,96]. These findings are of relevance in formulating health care policies and in allocative decisions in public health and government-funded projects to combat cataract blindness especially in low to middle income or developing countries. Indeed, according to current evidence, MSICS is the procedure of choice in various humanitarian campaigns aimed to reduce cataract backlog in poor and underprivileged communities[92].

Instrumentation requirements of MSICS

The successful outcome of MSICS depends upon a surgeon's skill rather than expensive machinery. The instrumentation requirements for MSICS are minimal and include consumables like disposable tunnel knives, irrigating solutions and ophthalmic viscoelastic devices. Newer methods of MSICS may also require the use of an ACM, phaco-fragmentation

devices like a nylon loop, nuclear trisector, *etc*, which are reusable. These help in reducing the overall cost of this surgery and making it a popular choice for resource-constrained centers. Since most technological advancement is industry-driven, innovative instrumentation for MSICS has not gained global popularity. Newer advances in smaller incision construction, nuclear management, and astigmatic correction with smart incisions can herald a boost in utilization of MSICS worldwide[50,84]. Healthcare is a major contributor to greenhouse gas emissions and environmental pollution. With increasing focus on development of sustainable technology minimizing carbon imprint, MSICS is a beacon to more-environment friendly surgery that reduces the use of paper, plastic, and energy[19].

TRAINING OF MSICS

Simulation for training of MSICS has recently picked up a rapid pace on the global scale[99]. Wet lab and virtual reality-based training results in shorter surgical learning curve, better surgical outcomes, lesser complication rates, increased surgeon confidence, better tissue handling and reduced intra-operative time. Traditional methods of training include use of animal eyes like goats' eyes, cadaveric eyes, artificial silicone eyes *etc.* The COVID era brought an increase in use of existing methods and newer innovative ideas for surgical training including use of simulators like EYESi (VRMagic, Haag-Streit, Switzerland), MicrovisTouch (ImmersiveTouch, Chicago, IL, United States), PhacoVision® (Melerit Medical, Linkoping, Sweden), and the HelpMeSee Eye Surgery simulator (HelpMeSee, Inc., New York, United States)[99-103]. However, most of the simulators available in the market are for phaco. The HelpMeSee simulator is programmed for MSICS as well as phaco, and a study showed that surgeons trained with simulators may perform better than conventionally trained surgeons, as simulator scores also offer feedback to trainee surgeons[103].

Two- and three-dimensional videos have also gained traction over time as valuable addendum to training materials with studies showing greater reliance on e-learning by medical professionals and YouTube videos helping both senior and junior ophthalmic surgeons[104,105]. Also, MSICS and ECCE are seen as stepping stones in a surgeon's journey towards mastery of phaco and are proven to ease the learning curve of phaco[18]. To standardize teaching and to objectively assess the proficiency of trainee surgeons, the International Council of Ophthalmology has developed the SICS Ophthalmic Simulated Surgical Competency Assessment Rubric. This is a validated surgical education and assessment tool and can guide young surgeons while progressing to live surgeries[106].

IMPORTANT RANDOMIZED CONTROLLED TRIALS FOR MSICS

Despite key differences in surgical techniques (Table 2), published studies have established comparable results and complication rates of MSICS and phaco, and both procedures have been shown to have similar efficacy and safety for visual rehabilitation[107]. A study conducted in Nepal on 108 patients showed that phaco and SICS had good visual outcomes with low complication rates with SICS being the faster and less expensive option[83]. Literature also supports MSICS as a preferred procedure for intumescent, mature and hard cataracts for resource-deficient settings[98,108]. Improvements in MSICS techniques like the use of ACM and viscoexpression results in earlier visual rehabilitation, with the phacosandwich being more effective in management of harder nuclear cataract[55]. Satisfactory outcomes are also noted in ocular inflammatory conditions like Fuch's heterochromic uveitis[109].

A systematic review and meta-analysis by Gogate *et al*[84] included 11 comparative studies comparing the safety, efficacy, and expenses of MSICS *vs* phaco. The postoperative uncorrected (UCVA) and best-corrected visual acuity were comparable between techniques with no statistical difference in endothelial cell loss during surgery. The incidence of intraoperative and postoperative complications were also not significantly different. Time efficiency and comparable outcomes were confirmed by studies in Nepal and in India[95,110,111]. In comparison with ECCE, MSICS is shown to have comparatively better visual outcomes[112]. MSICS group achieved unaided visual acuity of 6/12 or 6/18 or better compared to conventional ECCE.

Although it is generally accepted that phaco has better short-term visual outcomes than MSICS, studies comparing short-term visual outcomes of phaco with MSICS are often affected by inadvertent case selection bias; hence, it is difficult to quantify the difference[113,114]. Phaco has the advantages of less mean corneal astigmatism, less AC inflammation, and better UCVA in the immediate postoperative period. A study conducted on 400 patients in India showed comparable efficacy between the two surgeries with better visual outcome at 6 weeks for phaco[115]. MSICS usually results in statistically greater astigmatism compared to phaco, and UCVA of 6/9 or worse, however, near UCVA may be better. Functional and anatomical outcomes at one month after surgery are comparable for both MSICS and phaco techniques [84,95].

As stated, astigmatism in MSICS has been countered by various maneuvers like a change of incision site, shape, size, architecture and placement of sutures[116]. On comparing various sites of surgery, the temporal approach for MSICS is reported to have less postoperative astigmatism and better UCVA than a superior approach[117]. X-pattern sutures were preferred to the horizontal sutures to reduce SIA[118,119]. Long-term data comparing the astigmatic outcomes of SICS and phaco are lacking, although the use of cautery in MSICS may not be associated with a higher post-operative SIA[28, 107]. Similar astigmatism was seen irrespective of the mode used for nucleus delivery in MSICS[55].

Studies show that endothelial loss is greater in older patients with hard nuclear cataracts when the eyes undergo phaco, as compared to MSICS. In MSICS, the continued BSS infusion-assisted nuclear delivery technique is proven to reduce endothelial cell loss compared to viscoelastic-assisted nuclear delivery, as per studies by Morya *et al*[64] and Singh *et al*[120]. With regard to IOP, both phaco and MSICS led to significant and similar IOP reduction 6 months postoper-

Table 2 Key Differences between manual small incision cataract surgery and phacoemulsification

Criterion	Manual small incision cataract surgery	Phacoemulsification
Anesthesia	Peribulbar, subtenon, topical augmented with subtenon	Topical, peribulbar, subtenon, topical augmented with intracameral
Superior rectus bridle suture	Optional	Not required
Conjunctival peritomy	Optional	Not required
Incision size	2-12 mm	Usually < 3 mm
Anterior capsulotomy	Can-opener, envelope, CCC	CCC
Viscoelastics	Usually low viscosity dispersive or cohesive	High viscosity dispersive required for harder cataracts
Nuclear removal	Wire vectis, Blumenthal, viscoexpression, hydroexpression, Fishhook, snare (nuclear fragmentation)	Ultrasonic emulsification and aspiration
Cortex removal	Simcoe cannula and modifications	Coaxial or bimanual automated, simcoe cannula less commonly
Machine dependence	No	Yes
Overall costs	Lower	Higher

CCC: Continuous curvilinear capsulorhexis.

atively (2.7 ± 2.9 mmHg *vs* 2.6 ± 2.6 mmHg, respectively) and caused comparable changes in the AC and angle parameters [121]. Mansoori *et al*[122] showed comparable IOP reduction at approximately 1.5 year follow up with phaco and MSICS combined with Mitomycin C-augmented trabeculectomy (13.9 ± 2.98 mmHg *vs* 14.1 ± 4.12 mmHg). An RCT again proved an IOP drop of 7.5% to 8.7% after MSICS[64].

Among the trials comparing phaco and SICS in terms of IOL implantation, phaco has shown proven advantages with ease in use of topical anesthesia, lower PCO rates, and lower SIA[107,112,115]. The recent use of square edge intra-ocular lens has shown considerable reduction in PCO rates in MSICS[123,124]. There are no randomized controlled trials describing the comparison in the rates of late-onset postoperative endophthalmitis. In addition, there is no evidence whether outcomes after the management of these cases favor one procedure over the other.

CONCLUSION

MSICS is a cost-effective and efficient procedure for cataract removal, especially in resource-limited settings. It involves creating a small, self-sealing scleral tunnel incision to remove the cataract and implant an IOL. Unlike phacoemulsification, MSICS does not rely on advanced machinery, making it accessible in rural and underserved areas. The incision is typically larger than that in phacoemulsification, but it is possible to perform MSICS through incisions as small as 2 mm as well. Surgeons use manual techniques to optionally fragment, and extract the cataractous lens through the scleral tunnel. MSICS provides excellent visual outcomes comparable to phacoemulsification when performed skillfully. The procedure has a short learning curve, making it ideal for simulation-aided training of ophthalmologists to meet the demands of high-volume settings. MSICS also minimizes surgical costs, benefiting patients in low-income regions. Postoperative recovery is generally quick, with minimal complications when proper aseptic techniques are observed, while controlling costs and carbon footprint. MSICS has a proven track record of success in the past, and is commonly performed even today in the era of machines. Recent improvements in the MSICS technique make it a true surgery for the future, with the potentially unlimited possibility of innovation. Overall, MSICS is a valuable technique for addressing the global burden of cataract blindness and a valuable resource for every ophthalmic surgeon to have in their armamentarium.

FOOTNOTES

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REVIEW

Artificial intelligence in medicine: Current applications in cardiology, oncology, and radiology

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Abstract

In this article, artificial intelligence (AI) usage and its benefits in medicine are reviewed in the oncology, radiology, and cardiology fields. The relevant literature was searched in PubMed and Google Scholar using the words "Artificial Intelligence", "Artificial Intelligence in Medicine", "Artificial Intelligence in Cardiology", "Artificial Intelligence in Oncology", and "Artificial Intelligence in Radiology" for the last 10 years. This article covers the AI's current implications in daily practice, discussing its advantages and disadvantages based on the findings. AI's effect in medicine for reducing workload, diagnosis, time management, and drug dosing is going to be reviewed especially in radiology, oncology, and cardiology fields as well as general usage of AI in addition to important highlights. Lastly, this minireview evaluates the current challenges of AI technology in medicine and how clinicians should work with this emerging technology.

Key Words: Artificial intelligence; Medicine; Radiology; Oncology; Cardiology; Management; Diagnosis

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Core Tip: Artificial intelligence (AI) is the ability of a digital computer system to perform tasks commonly associated with human beings. In this article, AI usage and its benefits in medicine and its specialties are reviewed.

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INTRODUCTION

Artificial intelligence (AI) is the ability of a digital computer system to perform tasks commonly associated with human beings. This term is often applied to systems that can reason, discover meaning, generalize, or learn from experience like humans[1]. In 1950, Alan Turing developed the Turing Test, thus making the foundation of AI technology and is being remembered as the "father of AI"[2]. Since the Turing Test, there has been massive development in AI with emerging technologies and methods such as machine learning (ML), convolutional neural networks (CNN), deep learning (DL), and large language models. Especially with the introduction of the ChatGPT in November 2022 by OpenAI, AI technology has made its way into our everyday life from asking simple questions to trying to manage complicated situations. ChatGPT has become the fastest growing internet app gaining 100 million users in two months[3].

In medicine, AI was first described as the MYCIN program in 1977 by Stanford University, using a rule-based expert system to help with therapy selection and dose calculation in cases of bacteremia[4]. Since MYCIN, AI algorithms in medicine have evolved to complex and detailed structures for clinical use. Between 2013 and 2016, AI was most used in diagnostic imaging, genetics, electrodiagnosis, and monitoring[5].

AI has diverse applications differing from operating rooms to emergency procedures or appointment-making to diagnosing patients, all in favor of a much elevated level of efficiency in daily practice. AI can do routine procedures such as data processing, dosage calculation or multi-drug combinations, and immunization schedules for children so that doctors' workload can be lighter and they can work more on creative things to make developments in their jobs and communicate with patients[6]. Since experience is a very important factor for doctors to make the right decisions when treating a patient or for surgeons to perform surgeries more accurately, AI can work on various data and can help reduce the factor of experience when it comes to doctors' performances[7]. When examining a patient, AI can work on patients' data to search for possible diagnoses by making entries of patients' complaints and assisting doctors[8] (Figure 1). Especially in emergency departments, acting fast and seeing patients in the most efficient way is very important. With AI, the average length of stay can be dramatically reduced. Also, sources and staff can be used more efficiently[9].

Another issue that affects doctors' work efficiency is malpractice cases. Fear of these cases can make doctors work more cautiously and this can affect the quality of the service that they are going to give and jeopardize patients' lives. With the help of AI, malpractices can be foreseen and therefore prevented. AI can calculate the possibility of malpractice and show alternative ways of treatment to avoid it. Also, AI can present non-biased evidence when it is needed in malpractice cases [8].

AI can be a tool in a very broad spectrum, reducing morbidity such as diagnosing diabetic retinopathy[10] or helping with higher healthcare costs and mortality by defining nosocomial infections[11], which can affect 100 million patients per year[12]. Diabetic retinopathy is affecting 34.6% of the diabetic patients and is a huge reason for morbidity. AI has demonstrated success in early diagnosis of diabetic retinopathy. Researchers have programmed a DL algorithm for scanning retinal fundus images for diabetic retinopathy and the operating point selected for high sensitivity. Optimized for high sensitivity, the algorithm achieved 97.5% and 96.1% sensitivity and 93.4% and 93.9% specificity across the two validation sets[6]. Nosocomial infections are a reason for mortality and morbidity in hospitals. Also, they raise the cost of health care rapidly. All around the world, nosocomial infections affect an estimated 100 million patients per year[7]. Therefore, with being a serious and global problem, diagnosing and recognizing nosocomial infections early is very important. AI can help monitor patients' vital signs and warn health workers about nosocomial infections. In a study, researchers combined medical knowledge with fuzzy theory AI method and created a monitoring and infection identification system called Moni/Surveillance in Vienna General Hospital. The usage of this AI system showed promising results[8].

In this article, we will review the applications of AI as well as its limitations which are derived from these technologies, mainly focusing on the areas of cardiology, oncology, radiology, allergy-immunology, and infectious diseases. The relevant literature was searched in PubMed and Google Scholar using the key words "Artificial Intelligence", "Artificial Intelligence in Medicine", "Artificial Intelligence in Cardiology", "Artificial Intelligence in Oncology", and "Artificial Intelligence in Radiology" for the last 10 years (published between April 2015-April 2025). Articles with titles that do not include these keywords are not screened.

AI IN CARDIOLOGY

Cardiologic diseases are mostly mortal, morbid, chronic, heterogeneous, slow, silent, and regressive but with rapid and life-threatening consequences. Therefore, AI methods such as DL, CNN, linear regression, or tree-based decisions have much potential in cardiology[13].

In cardiac evaluation, echocardiography and electrocardiography are essential but interpretation of the received data from these methods can be difficult because of the artifacts and errors. Especially, detecting conditions such as premature

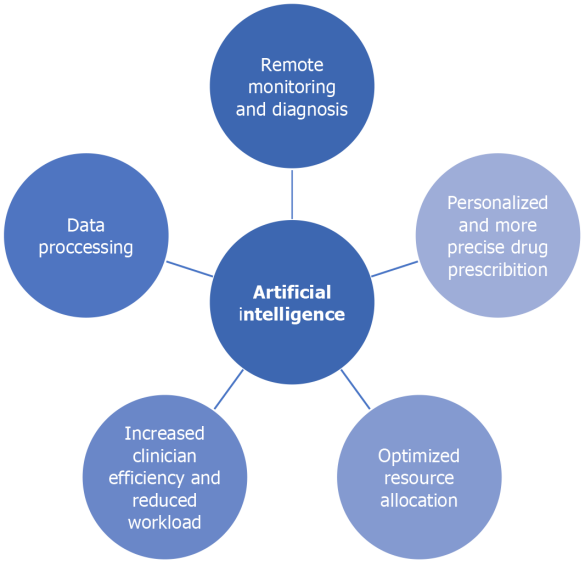


Figure 1 Benefits of artificial intelligence in medicine. When examining a patient, artificial intelligence can work on the patient's data to search for possible diagnoses by making entries of the patient's complaints and assisting doctors.

beats, atrial fibrillation, ventricular hypertrophy, non-sinus rhythms, and pacemaker dysfunction is very difficult. Thus, clinicians can use the help of technologies derived from AI. With this purpose, researchers from the Mayo Clinic have developed an AI algorithm using a CNN called AI-ECG. The study included 720978 adult patients aged 18 years or older with a standard 12-lead electrocardiography (ECG) performed at the Mayo Clinic ECG laboratory between 1993 and 2017. These ECG samples have been re-evaluated with AI-ECG for determination of primary and secondary rhythms, axis deviation, and chamber enlargement, and detection of atrioventricular and intraventricular conduction delay, myocardial ischemia, and waveform abnormalities. AI-ECG showed promising results in researched conditions[14]. Also, another study using a Food and Drug Administration (FDA)-approved AI system called Viz.ai showcased promising results in diagnosing hypertrophic cardiomyopathy (HCM). HCM is one of the main causes of sudden cardiac death in youth and its prevalence is approximately 1 in 500. Early diagnosis is the key to preventing death. Viz.ai has identified HCM with a sensitivity of 68.4% and specificity of 99.1%[15]. Therefore, AI has much potential to reduce artifacts and help clinicians make more accurate comments and diagnoses based on ECG data.

Ultrasonographic echocardiography is also commonly used in cardiology but there is a high chance for error because the quality of the echocardiogram image is influenced by the clinician's experience and competence. It is harder to present generalized data in echocardiography. Therefore, AI models have been developed regarding this issue. AI can help reduce noise and improve navigation of the ultrasonography probe. Some of AI models have already been approved by the FDA in the United States of America[16].

Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement (CMRIG) is a technique used for identifying ischemic or fibrotic tissue in the heart. It can be used in the diagnosis or management of myocardial infarction, myocarditis, sarcoidosis, amyloidosis, hypertrophic cardiomyopathy, and diabetic cardiomyopathy. The biggest disadvantage of this technique is the need for intravenous (IV) contrast agent injection. Contrast agents cannot be used in patients with kidney failure or pregnancy due to the increased risk of nephrotoxicity. Also, gadolinium administration raises the cost of the procedure significantly. To overcome these obstacles, a virtual native enhancement (VNE) imaging technology was developed using AI. In a study conducted on hypertrophic cardiomyopathy patients, VNE showed better quality images than CMRIG without the need for an IV contrast agent with less cost. VNE has much potential to replace CMRIG and to help reduce the side effects caused by contrast agents[17].

Different from other fields, cardiology uses biomarkers such as cardiac troponins, creatine kinase, D-dimer, myoglobin, and cardiac enzymes. These biomarkers are essential for diagnosis, treatment, and acute management. AI can help use biomarkers more effectively when assessing each patient individually[18] and choosing the right biomarker for the highest specificity and sensitivity while classifying the data according to clinical cases[19].

Also, cardiac conditions and treatments need to be evaluated for a long time. Patients must come in regularly and the clinicians must modify the treatment by calculating the patients' overall health. AI can help clinicians when planning the right and individualized treatments[20] and assessing the patient's condition when deciding on an invasive procedure [21].

AI IN ONCOLOGY

Cancer is a worldwide and serious health problem. Cancer incidence is rising with the elevated levels of radiation in daily life, pollution, and chemicals. In 2022, cancer prevalence in Asia is 6.5 million and in Europe is 3.5 million. And by the time of 2050, its prevalence was predicted to almost double[22] (Figure 2).

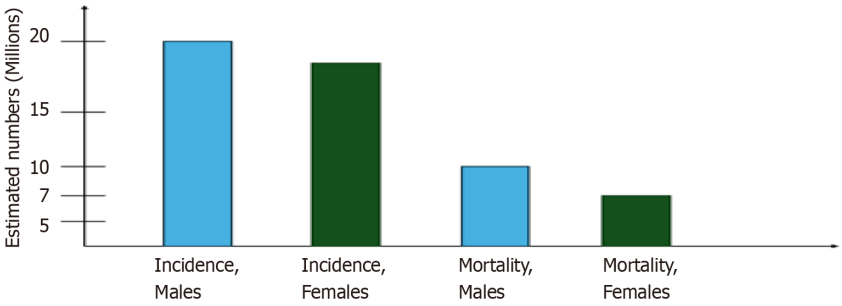


Figure 2 Estimated numbers of cancer cases in 2050. By the time of 2050, cancer prevalence was predicted to almost double in Asia and in Europe.

With this alarming number of cases, early identification of cancer is more important. Considering that most of the cancer cases are asymptomatic, clinicians can use the help of technologies like AI. Also, when patients are diagnosed, they need excessive care and treatment over a prolonged period of time. AI can help with the diagnosis, choosing the right treatment regime, and following the patient's health data.

For the diagnosis of cancer, imaging is a must. Especially, ML and image processing methods have much promise in this area due to examining mass amounts of screenings for abnormal findings and detecting them more accurately with cross-referencing. AI can be helpful in cancer imaging with monitoring, detection, segmentation, classification, and characterization of the lesions. Different from MRI and computed tomography (CT), AI can offer more qualitative data rather than quantitative data[23]. In cancer imaging, AI has a great prospect in a very broad spectrum from helping clinicians identify early gastric cancer in endoscopy images[24] to generating three-dimensional (3D) images from positron emission tomography (PET) screening[25], all for better understanding of the cancer diagnosis and identifying malignant masses as soon as possible to reduce the mortality. These new technologies can be the key to understanding cancer's pathophysiology and carrying the treatments into the next step[23] (Figure 3).

Lung cancer is one of the deadliest cancers of all time and the number of new cases estimated is very high, along with breast cancer[26]. Thus, there has been great interest in using new tools like AI for the identification and classification of lung cancer.

The first step of lung cancer diagnosis is scanning chest radiograph images and detection of nodules. After detection, clinicians can suspect lung cancer. AI-assisted image analysis with ML has demonstrated efficacy in detecting nodules that might otherwise escape radiologists' detection[27]. After detection, more accurate classification of the nodules or assessing the genetic figuration of the mass can carry therapies like immunotherapy into the next level. Usually, a biopsy is used to differentiate tumor type, but tumors can be heterogeneous. Therefore, biopsy is not always reliable considering taking sample tissue from only one area[23]. More overall knowledge about the assessment of the mass can give clinicians the needed insight into the patient's status. In a study, a DL algorithm has been trained to extend the assessment of nodules rather than using the traditional classification such as solid, part-solid, non-solid, and calcified nodules[28]. AI has brought depth when looking into the characters of nodules, thus making the way to improving the selected therapy's outcome.

Also, immunotherapy is often used in lung cancer, and it is chosen based on the tumor's gene expression. ML algorithms can be trained using pathology reports and can define different genetic expressions in lung cancer easily. It is a huge step for making better-personalized immunotherapy. It can lighten clinicians' diagnostic burden while improving the prediction of cancer susceptibility, mortality, and recurrence up to 25%[29].

Breast cancer is the most common cancer in the United States and it has the highest estimated chance of incidence[26]. Mammography is a useful tool for screening breast cancer. It can detect clusters, masses, or calcifications. And with BIRADS classification, clinicians can have an insight into the prognosis. Although mammogram findings must be proven with other screening methods, it is still the key to diagnosing breast cancer[30].

In a study, CNN has been used to classify the breast tissue as normal or mass tissue. CNN has been trained using 168 biopsy-proved breast cancer and 564 normal breast images approved by experienced radiologists. The study showed that CNN worked with a true positive fraction of 90% and false positive fraction of 31%[31]. Besides that, there are multiple software programs showing promising results in identifying pathological findings and diagnosing breast cancer[32]. Also, when evaluating a mammogram, increased density of breast parenchyma is an issue. Because increased density can hide masses and make it more difficult for the clinician to interpret the mammogram more accurately. Breast density increases as people age, which is another risk factor for breast cancer. DL can grasp a better understanding of identifying masses in more dense parenchyma and shows much potential for improving the diagnosis of patients[33].

Mammography is also used in screening. Screening programs for breast cancer identification exist worldwide and many clinicians perform these programs[34]. Screening programs with mammograms provide the chance for earlier diagnosis and early start for adjuvant therapy, hence reducing the mortality rate up to 68%[35]. However, these often usage of mammograms can have negative outcomes. In a study, researchers showed that screening with mammography leads to 132 over-diagnosed breast cancer cases in 10000 women[36]. Excessive usage can also lead to misusage of sources and increased workload for clinicians. Therefore, with these situations, an opportunity for AI arises for reducing the workload and over-diagnosis. Triaging the mammography findings with AI software and consulting the radiologist on only needed cases is reducing the workload and makes the performance of the clinicians better. AI can grade the findings as more or less likely to be diagnosed as cancer and can work coherently with the clinicians[37,38]. However,

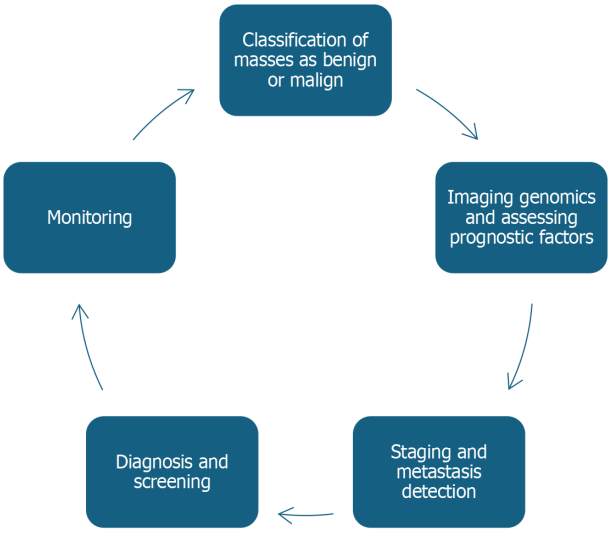


Figure 3 Artificial intelligence in cancer screening. New artificial intelligence technologies can be the key to understanding cancer's pathophysiology and carrying the treatments into the next step.

implementing AI does not always bring positive outcomes. In a study, evaluating mammograms with computer-aided detection is associated with an increased rate of biopsy but on the contrary, reduced accuracy of findings[39]. AI shows great potential in interpreting mammograms, but it should be used as a tool, work coherently to enhance the performance of clinicians, and not be overthrown or ignored when it comes to making decisions about patients' care.

In oncology, AI is mainly being used in cancer diagnosis, but it is surely not the only area for it. AI can detect metastasis, evaluate the genetic or hormonal structure of the mass, or predict the patient's survival and recovery.

In a study, a neural network model was accomplished to determine the isocitrate dehydrogenase (IDH) mutation status of gliomas from MRI with an accuracy of 82.8%. IDH mutation means a longer chance of survival in glioma patients and can potentially alter the treatment of choice. With neural networks, IDH status can be assessed without invasive procedures[40]. Another prognostic factor for gliomas is the deletion of chromosome arms of 1p/19q. The existence of this deletion is linked with better therapy response and a higher chance of survival without relapses. Best performing CNN predicted the chromosome deletion with a 93.3% sensitivity and 82.22% specificity from MRI[41]. With this accomplishment, deletion status can be assessed without biopsy, creating a chance for more accurate treatment and increasing the life expectancy in low-grade glioma patients.

Another factor for the prognosis of cancer patients is whether the primary lesion metastasizes or not. Especially in breast cancer due to anatomical relatedness, axillary lymph node metastasis is a very important prognostic factor and helpful for assessing the mortality or predicting the chance of metastasis in other regions[42]. In a cross-sectional study that evaluated 32 DL algorithms, 7 algorithms showed greater discrimination of metastatic tissue in biopsy samples than a panel of 11 pathologists[43].

In addition to these points, artificial neural network algorithms have proven effective in predicting delayed discharge or readmission after laparoscopic colorectal surgery. With these results, neural networks have the potential to create an ideal predictive tool for postoperative patient recovery[44].

AI IN RADIOLOGY

Since the discovery of the X-ray technology by Roentgen, imaging technologies have been a huge part of medicine. With the advancement in technology, various imaging techniques such as PET, CT, and MRI are being used by clinicians around the world. Thus, radiology is one of the fundamental specialties in health care. Clinicians use imaging for diagnosis, screening, examining the patient, or selecting the therapy. In 2023, 45 million imaging tests were reported in the United Kingdom, with an increase rate of 2.2%[45]. With the increasing number of imaging units and the ordered scans[46], radiologists face a variety of problems. They experience higher rates of burnout, unreasonable amount of workload, and inadequate workflow efficiency[47]. On top of that, there have been several reports from various countries in the past years about radiologist shortage in medical care[48-50].

With the launch of ImageNet in 2009, AI technologies have reached a new level when it comes to classifying, identifying, and segmenting visual databases, as well as recognizing patterns and associating them as certain indicators. ImageNet can also function as a pool for annotated datasets for CNN training[51]. Therefore, cooperation with AI became inevitable for helping radiologists. Between 2015 and 2019, over ten thousand papers have been published regarding AI and radiology with cancer imaging being the most focused area[52]. There are currently 48 AI programs for abdominal imaging, 46 for breast imaging, 67 for cardiac imaging, 91 for chest imaging, 41 for musculoskeletal system imaging, and 112 for neuroradiology, which were all approved by the FDA[52,53] (Figure 4).

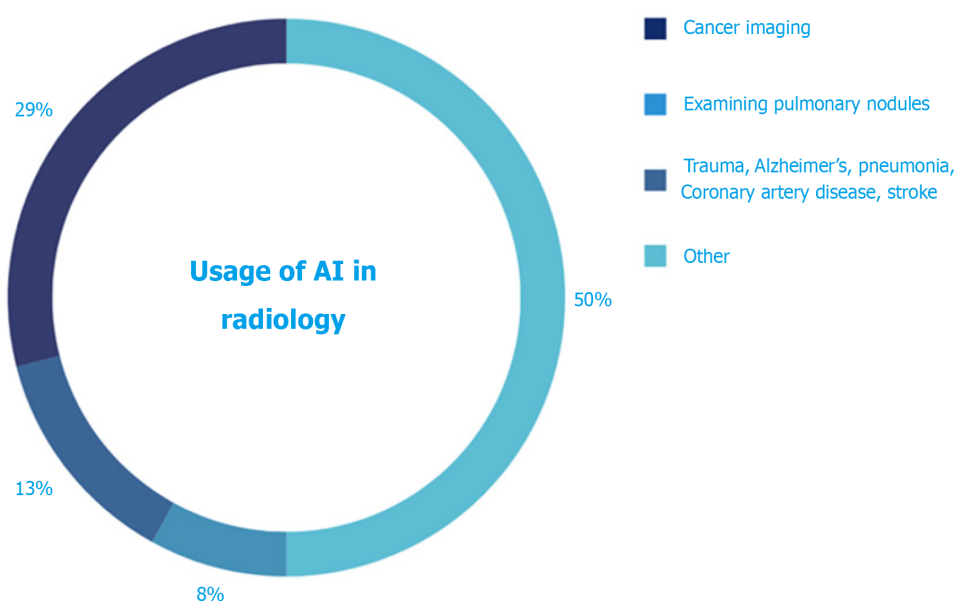


Figure 4 Usage of artificial intelligence programs approved by the Food and Drug Administration in radiology. AI: Artificial intelligence.

For the management of the patient in emergency departments, radiological imaging is a must. Clinicians need to act fast to diagnose and triage the patient since it is crucial to patients' survival. It is important to identify pathologies from images or to eliminate the artifacts by recognizing them and choosing the right procedure of imaging for the right patient. With the need to quickly act the pressure of dealing with mortal situations, and long and overnight working hours, clinicians working in emergency departments are more prone to making wrong or delayed diagnoses. Clinicians seem to make diagnostic errors mostly in patients with fractures (44%), myocardial infarctions (7%), or intracranial bleeding (6%), with 15% of the errors resulting in severe harm or death[54]. Implementing AI in daily practice can help clinicians in most common cases presenting to the emergency departments such as pulmonary embolism, stroke, acute abdominal pain, and fractures[55].

AI tools are open for integration into the diagnosis-making by alerting the clinicians 24/7 when suspicious findings are detected for stroke, intracranial hemorrhage, or pulmonary emboli, hence guiding the clinician for better management of the patient[56]. Chest radiography is one of the most used radiological imaging modalities in emergency departments. Evaluation of the chest radiography most often requires the attention of radiology residents; however, it is not possible to reach that due to working hours or staff shortage. In a study evaluating AI's accuracy for chest radiography, AI performed equally well with radiology residents but outperformed non-radiology residents[57]. AI can work 24/7 in the background reducing the need for radiology residents and lightening the workload. AI technology has proven successful when assisting clinicians in evaluating CT pulmonary angiography by catching 19 pulmonary emboli cases missed by clinicians, therefore acting as a double-checking standard in clinical practice[58].

For musculoskeletal imaging, AI has proven effective for classifying distal radius fractures from frontal and lateral radiographs when it comes to identifying fragment displacement or joint involvement as well as eliminating artifacts that usually stem from bone superimposition or osteoarthritis[59]. Also, using standard measurement techniques for anatomical landmarks such as hip-knee angle, tibia/femur or leg length, and pelvic obliquity is essential when diagnosing musculoskeletal diseases. Automating these measurements with AI is a huge step forward saving workforce and energy[60].

The reduced quality of radiographic imaging can be a huge problem for clinicians. DL programs have been trained to classify MRI' quality as acceptable or unacceptable[61]. For MRI, it is even possible to assess fetal MRI which artifacts are most likely to occur due to limitations[62], giving insight to the clinician on how to evaluate or even decide to dismiss the image.

PET is a widely used imaging technique with proven clinical benefits. PET imaging has extended its benefits with the synergy between new technologies such as the introduction of PET/CT scanners. PET image reconstruction is another method for PET images to be open for interpretation and ready for clinicians. With PET image reconstruction, cross-sectional images that stem from radiotracer distribution can be provided as well as resolution of the images can be enhanced. There are several mathematical formulations for this cause[63]. The potential in DL and CNN for doing monotone mathematical calculations in rapid speed and accuracy while being open for training and modification, made AI a suitable technology for PET image reconstruction in the path of getting a more accurate radiological image. For this purpose, different AI algorithms have been introduced with the technology of CNN or DL. These algorithms differ from each other in the aspects of interpretability, suitability for 3D image reconstruction, inference time, generalization, and expected image quality if within training distribution. Each algorithm has its advantages and disadvantages[64]. Especially, DL algorithms have been found successful when it comes to metal artifact reduction that can stem from prosthetics or implants. Different DL and metal artifact reduction algorithms can be combined for better image reconstruction for PET images or to enhance the quality of CT imaging[65,66]. However, the need for different algorithms

for different imaging techniques such as CT or MRI, or for different sole purposes such as artifact reduction raises the problem of instability. AI algorithms can produce other artifacts stemming from programming or training data sets, making it difficult to reach a generalized universal image quality[67]. CNN-based PET image reconstruction programs may produce more artifacts. On the other hand, DL-based systems are harder to program with needing larger training data sets. Therefore, the need for new technologies and emerging AI algorithms is still there. A new algorithm integrating a deep image prior framework has been introduced, and it is superior to DL reconstruction programs and eliminates potential biases that arise from different training data sets[68].

AI in radiology is not only effective in artifact reduction or image reconstruction but also in the synthesis of images. With the introduction of cycle-consistent adversarial networks[69] and U-Net[70] algorithms, AI for image synthesis has reached a new level. There are several DL algorithms for the synthesis of pseudo-CT, synthetic MRI, and synthetic PET, and they all show great promise in medical usage[71]. Even though they have their advantage and disadvantages, a study conducted comparing cycle-consistent adversarial networks and U-Net algorithms in pseudo-CT/MRI synthesis showed that the U-Net algorithm showed superior performance, especially in pseudo-CT[72]. These CNN and DL algorithms were found to be successful for image synthesis and also applicable for more vulnerable patient groups such as pediatric patients. A study comparing CT and synthetic CT (sCT) quality in bone elements of sacroiliac joints in children found that there is no significant lowering in quality between sCT and CT. On top of that, sCT performed even better when it comes to showing cortical delineation[73]. DL also showcased the potential to reduce given radiation dose to patients by up to 75% with deionizing algorithms[74]. AI has a key potential for the next step of radiological imaging. They are also adaptable and changeable to need, such as reprogramming the algorithm[75] or adapting to different imaging techniques such as fluoroscopy[76] (Figure 5).

Another usage of imaging technologies such as MRI and CT is to plan radiotherapy. Clinicians evaluate the lesions with CT and MRI and decide the radiotherapy protocol and dosing. However, working with two different imaging techniques comes with errors and interpretation mistakes. To reduce the workload, cost, and radiation doses, clinicians are thinking about a new radiation therapy that uses solely MRI for treatment planning. When compared to procedures including CT scans, MRI-only protocol did not show any difference in the outcome of treatment planning and has a chance of replacing CT protocols[77]. On the other hand, with the development of AI technologies and not wanting to lose the advantages of CT imaging, researchers started using sCT from MRI in radiation oncology. sCT technology is applicable and useful for clinical use, eliminating unnecessary radiation doses as well as making it possible to evaluate the patient's condition from a broader perceptive. sCT algorithms apply in radiation oncology from brain to prostate lesions[78] or pediatric groups as well as adult patients[79].

AI shows great promise in cross-referencing studies; however, it seems that further study for the correct implementation of AI in clinical practice is much needed. According to an article, radiologists who use AI technologies on daily basis, experience higher burnout than the ones who do not. These rates have been associated with the higher expectancy of work performance from the radiologists who work with AI[80]. In a survey conducted by the European Society of Radiology, 47.6% of the responders do not use AI and 30.4% do not use AI at present but plan on using it in their daily practice. In the same survey regarding their workload status with AI in their practice, 51% of the responders accept increase while 49% accept decrease[81]. When evaluated, the impact of ML-based clinical decision algorithms has a positive impact on performance, especially in less experienced residents' daily practices compared to their senior colleagues, and overall AI does not make significant changes in 80% of the cases[82]. These data can derive from the fact that AI technologies need adaption for medical use. Implementing data processing technologies to medical images remains challenging. With the differences between nature images and medical images, scientists must find new ways to program CNN for optimal findings. Training CNN through transfer learning from large scale data has proven effective when researched on identifying lymph nodes and interstitial lung disease. With that, training the CNN from scratch or exploring different properties of training also has potential for achieving better outcomes[83].

AI APPLICATIONS IN OTHER MEDICAL FIELDS

Even though we focus mainly on the applications in cardiology, oncology, and radiology fields (Table 1), AI has much broader clinical applications in medicine. In this chapter, we will briefly highlight its applications in allergy- immunology and infectious diseases.

AI IN ALLERGY-IMMUNOLOGY

Allergy-immunology is a very sophisticated field with a large set of diseases, dealing mostly with chronic and multi-systemic conditions, thus attending both pediatric and adult patients. Allergic diseases are considered an umbrella term containing several diseases (rhinitis, urticaria, asthma, atopic dermatitis, *etc.*), and differentiating one from another is not always easy in clinical practice. Allergic and immunologic diseases have similar pathogenic pathways including cytokines like IL-5, IL4R, JAK1, and NR3C1. Identifying these cytokines and their role in pathogenesis with AI-driven targeting systems can open a new chapter in targeted immunotherapy and more accurate diagnosis[84]. AI research in allergy-immunology mainly focused on asthma, inborn errors of immunity (IEI), and atopic dermatitis. However, research on other conditions such as anaphylaxis, urticaria, and eosinophilic gastrointestinal disorders is emerging[85]. In asthma diagnosis, the main challenge is the differentiation from chronic obstructive pulmonary disease (COPD). Pulmonary function tests are not specifically discriminative, especially when it comes to diseases like asthma-COPD

Table 1 Purposes of using artificial intelligence in fields of cardiology, oncology, and radiology

Cardiology	Oncology	Radiology
Detecting rhythm and wave abnormalities in the electrocardiography	Lesion segmentation and classification	Reducing artifacts and noise
Diagnosing hypertrophic cardiomyopathy	Detection of CT nodules in the lungs	Synthesizing pseudo-images
Noise reduction in echocardiography	Assessing hormonal and genetic status of lesions	PET image reconstruction
Cardiac MRI using VNE technology	Improving mammography sensitivity	MRI radiotherapy programs only
Cardiac enzyme classification	Prognostic prediction and staging	Emergency room clinical assistance
Cardiac resynchronization therapy adjustment	Detection of metastases	Standardization of anatomical landmark measurements

MRI: Magnetic resonance imaging; VNE: Virtual native enhancement; CT: Computed tomography; PET: Positron emission tomography.

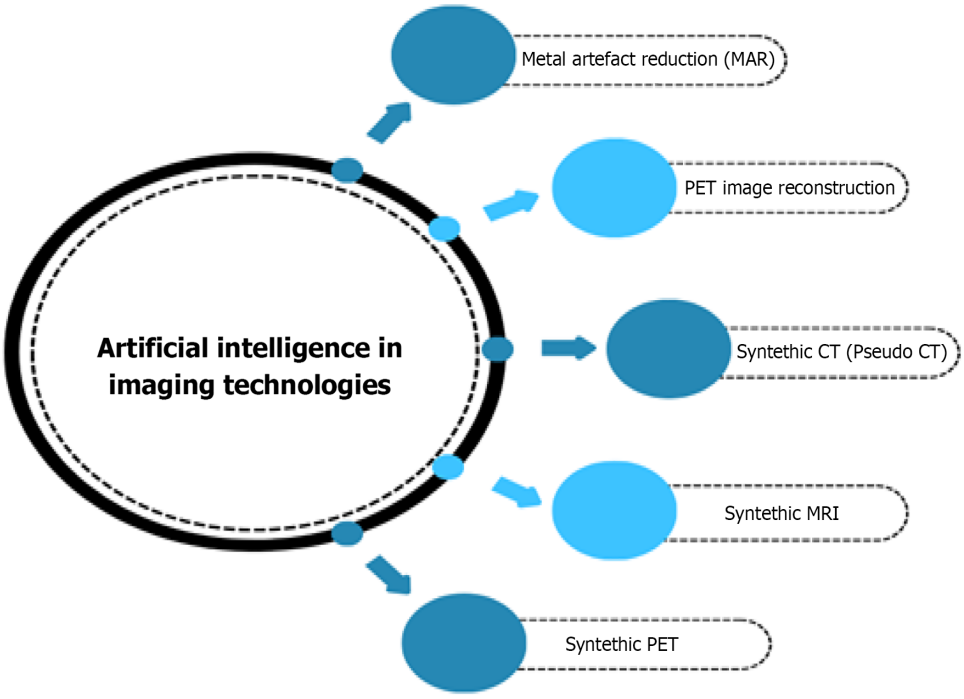


Figure 5 Artificial intelligence use in various imaging technologies. CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography.

overlap syndrome. Recurrent neural networks have proven to differentiate asthma from COPD with 68% accuracy and can work when complexity such as asthma-COPD overlap syndrome is presented[86]. In the prognosis of asthma, the main cause of morbidity and mortality is asthma exacerbations. Exacerbations need immediate care and diagnosis. The main solution for reducing exacerbations is the right prophylactic therapy and drug dosing by predicting the prognosis and quick evaluation. Researchers created a two-rule-based algorithm using electronic health data from patients, and the algorithm proved to identify asthma-related emergency department encounters with 95% specificity and sensitivity[87]. When calculating the patient's chance of presenting with asthma exacerbations, the Asthma Guidance and Prediction System is considered effective for predicting asthma attacks and reducing the median time of patient evaluation[88].

IEI are one of the causes of morbidity and mortality in children. Early diagnosis in IEI is much needed to protect the patients from "diagnosis odyssey" and ultimately reducing the performed tests for diagnosis while saving time[89]. Today, clinicians use the Joffrey Models 10 Warning Signs (JMF10WS) for suspecting IEI in a patient. However, JMF10WS criteria are still not enough to prevent delayed or underdiagnosis. Different AI models especially ML models can enhance the sensitivity of screening tests by adding factors such as typical IEI diseases, IgG/IgA/IgM levels, age, body weight, or lymphopenia[90]. Training AI algorithms in broader signs for IEI rather than only sticking to JMF10WS is promising for early IEI diagnosis.

AI IN INFECTIOUS DISEASES

Infectious diseases cause major handicaps in healthcare especially in public health. Prevention of infectious diseases is crucial in society for upholding greater standards of healthcare and prosperity. Clinicians lack new methods to diagnose and treat chronic infections known for years such as human immunodeficiency virus (HIV) infection and tuberculosis (TB) while struggling with antibiotic resistance and infections like severe acute respiratory syndrome coronavirus 2 thanks to modern-age medicine. Hence, there is a need for a new chapter in infectious diseases due to struggles coming from both pharmaceutical and clinical aspects of medical practice. The gold standard for diagnosis in almost every infectious disease is blood culture but incubation time for growth is approximately 24-48 hours. This period forces clinicians to use empiric antibiotics to avoid complications coming from the delayed start of therapy. Empiric antibiotic use increases antibiotic resistance and causes unnecessary drug usage. Predictive DL algorithms have been proven to classify blood samples as contaminated or not contaminated when trained to predict the existence of the most common pathogens (*E. coli, Klebsiella, S. aureus, Enterococcus, Streptococcus*), making it possible to diagnose bloodstream infections without waiting for a period[91].

TB is still a major health issue and has a unique multiple-phased prognosis, and it is difficult to choose which patient to give prophylaxis or treat. Latent TB (LTB) occurs when a patient does not have active TB (ATB) symptoms but has positive blood tests or tuberculin skin test (TST). The Centers for Disease Control and Prevention recommends annual screening in high-risk groups for LTB[92]. However, conventional skin and blood tests can lead to misdiagnoses because interpretation is hard to standardize. Also, the main reason for screening tests in LTB patients is their elevated chance of developing ATB. Clinicians must be alert in LTB patients so that they can diagnose ATB early and prevent comorbidities, and they need new technologies to detect ATB even before the patient's symptoms worsen. Diagnostic blood and skin tests have low positive predictive values down to 4.2% (in a blood test) and 3.5% (in a TST) when tested for ATB development percentage in LTB patients[93]. Despite these low predictive values in conventional testing, screening algorithms trained with sputum examination, TB symptoms, and chest radiography reached a 90% sensitivity for ATB screening among LTB patients[94]. Also, with the help of decision-tree-based algorithms, scientists achieved to distinguish peripheral blood mononuclear cells' gene expression levels based on their sensitivity to differentiate LTB and ATB. The algorithm detected *CXCL10*, *ATP10A*, and *TLR6* genes to have the highest sensitivity up to 71% and specificity up to 89%[95].

Antimicrobial resistance (AMR) is one of the major challenges in medicine, causing morbidity and mortality. With the excessive use of antibiotics or prophylactic treatments, AMR is rising as a major worldwide health problem. On the contrary, production of novel antibiotic agents is very low, therefore drawing attention to AMR as more of a serious handicap. To reduce AMR or fight with ML algorithms can predict which patient needs pre-exposure therapy for HIV infection[96], being a guideline for which patient to give prophylaxis, thus reducing excessive antimicrobial agent usage. Conventionally, an antibiotic resistance test is performed when a sample is obtained from patient to see if their pathogen is resisting to existing antimicrobial agents. Typically, these processes can take up to a minimum of 24 hours, which can be crucial for choosing a patient accurate treatment. In a study, an ML algorithm can successfully predict antibiotic resistance to the most common pathogens in urinary tract infections when trained based on a patient electronic health data such as demographics, past drug prescriptions, and past urine samples[97], ultimately reducing the time for choosing the most suitable drug prescription in treatment. In novel drug development, DL algorithms predict the genes that cause AMR[98], therefore leading to a more AMR-aimed perspective in the drug development industry. On the other hand, again DL algorithms have proven successful in detecting potential biosynthetic gene clusters[99], which is the main criterion in choosing which nature-derived material can be a candidate for antimicrobial drug development.

There are still so many AI studies in medicine even though we tried to cover as much as possible in certain areas, exploring AI technologies and how they can transform the medical practice. AI algorithms' applications and literature are broad including every inch of medicine from anesthesiology to nephrology and even psychiatry[100-102].

CURRENT CHALLENGES AND LIMITATIONS OF AI APPLICATIONS

The main challenge of AI in clinical use derives from its training technique. AI technologies like ML and DL need large data sets to function and the selection of these datasets can cause biased or limited outcomes of the program. Still, AI ChatBot's response derives based on sex or ethnicity, causing misleading or ineffective consultation in therapy selection [103]. Other than biased datasets, AI's predictive value drops in not common or overlooked diseases because of the lack of existing literature and data. In the training and functioning process, many AI algorithms work in a "black box" protocol, remaining unknown of their inner workings. This raises the issue of transparency and being close to easy modifications or receiving criticism when they make non-coherent or non-cohesive responses. Especially ChatGPT algorithm had a lot of backlashes regarding its tendency to hallucinate, a phenomenon referring to ChatGPT's unreal or heavily modified responses[104]. These responses can cause harm to the patients, raising the issue of malpractice. When evaluating ChatGPT's accuracy, 8% of the outcomes have been classified as completely wrong. Even though other outcomes did not cause any harm to the patient, they have the potential to jeopardize doctors' credibility[105]. Malpractice issues raise the need for regulations and legal limitations of AI use, highlighting governance as the other aspect of the implantation challenge. Other than malpractice, using AI can bring up issues as feud or impersonating. In some studies, AI is considered indistinguishable from human work[106]. It is crucial to bring up generalized regulations to AI systems so that they cannot be used without clinicians' supervising, therefore preventing misleading medical advice from mistrusted sources.

Implementing data processing technologies to medical images remains challenging. Especially for the use of AI in radiology, image processing algorithms still need broad modifications. With the differences between natural images and medical images, scientists must find new ways to program CNN for optimal findings. Training CNN through transfer learning from large-scale data has proven effective when researched on identifying lymph nodes and interstitial lung disease. With that, training the CNN from scratch or exploring different properties of training also has potential for achieving better outcomes[83]. However, today, the outcome of AI in image processing cannot be fully trusted. In other areas of medicine rather than image processing, this implantation problem remains an issue. Thus, most of the AI experiments or revisions on algorithm modifications are being made in non-clinical environments[107]. Clinicians only reach the final product and have little say during the creation process.

Other than limitations coming from algorithms' working protocol, implications of AI raise ethical, security, or trust issues. For using AI in clinical practice, patients' data must be shared with these algorithms. This raises cybersecurity issues and can ultimately violate the sacred trust between the clinician and the patient, which is the key to making the right diagnosis and treatment. Patients still trust their doctors rather than AI and are relieved to know that their doctors are the ultimate decision-makers in their treatment process[108]. Upholding this trust is crucial to maintaining high standards of clinical practice. Therefore, clinicians must not rely too much on AI technologies because it is easy and approachable but make decisions according to their own judgment.

POTENTIAL FUTURE DIRECTIONS AND UNRESOLVED ISSUES

When it comes to clinicians' point of view, challenges are coming from misinformation or prejudice. Many clinicians think that AI is going to steal their jobs or disqualify them. Especially, senior residents do not report any change in their daily practice coming from AI compared to their junior colleagues[82]. They are frightened to get used to AI technologies. Many healthcare workers must be educated to understand AI or how to use it while getting the most benefit. This needs organization and sources for education, making the transition to AI a much harder process. Some clinicians experience higher burnout rates when using AI[80] and 51% of them believe that AI is going to increase their workload rather than decrease it[81]. This attitude comes from patients' or hospitals' expectancy of faster and more efficient workflow when invested in AI.

CONCLUSION

AI is an emerging technology making its way into medicine and clinical use rapidly. In this article, we focused on its impact on the cardiology, radiology, and oncology fields. AI technologies like ML, DL, and CNN show great promise in diagnosis, treatment planning, prognosis assessment, and overall helping the clinician give the best care to the patient. However, AI is not a magical tool that can erase all the problems in medicine or cannot be used as the sole decision-maker. Clinicians must adapt to this new technology and learn to incorporate it into their practice. AI must be reevaluated in the light of clinical practice to overcome limitations. All factors such as patients, government, hospitals, and clinicians must be incorporated into the process. There are a massive number of papers in this area, many of them showing promise in cross-referencing studies. However, there is still much to do for corrective usage of AI in best interests of both the patient and the clinician.

FOOTNOTES

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REVIEW

Scoping review of micronutrient imbalances, clinical manifestations, and interventions

Kevan English, Christine Uwibambe, Pretty Daniels, Elfreda Dzukey

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Abstract

Micronutrients are fundamental to support and maintain normal physiological function. Deficiencies of these nutrients are a growing public health concern with potentially devastating consequences. An adequate diet of whole foods is the primary source of micronutrients; supplementation is sometimes necessary. Both deficiency and excess of these nutrients have adverse effects. Common deficiencies include iron, folate, iodine, zinc, and vitamin A, which can present clinically as a syndrome. Micronutrient deficiencies (MNDs) are common contributors to intellectual impairments, poor growth, perinatal complications, and increased risk for morbidity and mortality. Excess of a select few of these nutrients can result in conditions such as idiopathic intracranial hypertension and diarrhea. Interventions, including supplementation, fortification, and biofortification, can help combat MNDs. This article reviews some common micronutrient imbalances, their clinical manifestations, and treatment interventions.

Key Words: Micronutrient; Iron; Vitamin A; Vitamin B12; Fat-soluble vitamin; Water soluble vitamin; Vitamin C; Micronutrient deficiency

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Core Tip: Micronutrient deficiency is an emerging public health concern affecting more than 2 billion people globally. These deficiencies can contribute to poor growth and intellectual disabilities, which increase the risk of morbidity and mortality, particularly in developing countries. Risk factors vary by micronutrient deficiency. Early recognition and intervention by clinicians drastically decrease global mortality. This article reviews various micronutrient deficiencies, their clinical features, and treatments in detail.

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INTRODUCTION

Nutrition is a modifiable factor that can be targeted to promote optimal health and reduce disease risk throughout a lifetime[1]. A healthy diet contains all the resources needed to meet the body's metabolic demands[1,2]. Nutrients (macronutrients and micronutrients) are essential molecules required to sustain a healthy and prolonged life[2,3]. Macronutrients (carbohydrates, lipids, and protein) are needed in significant amounts to facilitate hormone creation, synthesis of molecules, energy production, and regulation of metabolic pathways[4]. In smaller quantities, micronutrients such as minerals, vitamins, and antioxidants are needed to aid biochemical processes such as enzyme reactions, protection against oxidative stress, and gene transcription[5,6].

Micronutrient deficiencies (MNDs) occur when an individual, regardless of reason, does not consume an adequate amount of food to meet their energy requirements[5-7]. Patients at risk include older adults, individuals with alcohol use disorders, pregnant women, vegans or vegetarians, and persons with increased requirements due to medical conditions or long-term drug use that alters metabolism, absorption, and excretion[7-9]. A sufficient amount is needed to support physiological processes and metabolism[10]. However, inadequate and excessive intake can be harmful and should be avoided[8-10]. MNDs continue to affect more than 2 billion people worldwide despite advances in technology and science[11]. In this article, we provide a scoping review of MNDs with a particular focus on fat and water-soluble vitamins, their clinical manifestations, and treatment. A few micronutrients in excess were expanded upon.

EPIDEMIOLOGY

Micronutrients are vitamins and minerals needed by the body in small quantities to meet its daily metabolic needs[11,12]. Deficiency occurs with low dietary intake of these compounds, and it is particularly prevalent in the developing world, affecting an estimated 2 billion people worldwide[11,13]. A lack of iron, folate, and vitamin B_{12} can result in anemia, which affects an estimated 42% of children under 5 years of age and approximately 40% of pregnant women[14,15]. Prevalence rates of MND are typically higher across South Asia and sub-Saharan Africa[16,17].

More than half of children under age five and more than two-thirds of women of reproductive age are deficient in at least one micronutrient[14-18]. Iron is the most common MND worldwide, which can result in anemia[19]. The World Health Organization (WHO) estimates that 25% of people worldwide have anemia and iron deficiency, the most common cause, is responsible for 50% of all cases[20,21]. Approximately 1.2 billion people worldwide suffer from iron deficiency anemia, with a higher prevalence in women and children[22,23].

These deficiencies are particularly prevalent in low-income countries, suggesting that poor sanitation, poor diet, and inadequate health care are major contributory factors[11,13,16,18]. Anemia and iodine deficiency disorders separately affect approximately 2 billion people in both developed and developing countries, and vitamin A deficiency is prevalent in up to 12% of low-income nations[13-19]. Muthayya *et al*[24] defined the hidden hunger index based on the national estimates of the prevalence of stunting, anemia due to iron deficiency, and low serum retinol concentration. Hot spots were found in South Asia and sub-Saharan Africa, where the highest prevalence of exists. MNDs are more common in developing countries, and clinical outcomes are more severe, given the lack of resources, including the quality of healthcare within these areas[12,14,16,18,20,22].

SOURCES AND CLINICAL MANIFESTATIONS OF FAT-SOLUBLE VITAMIN DEFICIENCIES/EXCESS

Fat-soluble vitamins, including A, D, E, and K, are energy-independent molecules that are essential to maintain adequate bodily function[25]. Their intake is almost exclusively from diet[26]. As such, deficiencies in fat-soluble vitamins are more likely seen in developing countries with limited resources than in industrialized nations[27]. These vitamins are classically absorption dependent on bile emulsification, pancreatic secretions, and a functional ileum[28]. Due to this fact, certain patient groups are at a higher risk for deficiencies, including those with liver disease, malabsorption syndromes with steatorrhea (*i.e.*, celiac disease and cystic fibrosis) intensive care unit patients, and patients with chronic mineral oil

intake[29-31]. Toxicity is less common for fat-soluble vitamins compared to water-soluble as fat-soluble molecules accumulate in fat[32]. The clinical manifestations of fat-soluble vitamin deficiencies and their dietary sources can be seen below.

Vitamin A

Vitamin A is a general term for a group of fat-soluble compounds consisting primarily of retinol and retinyl esters[33]. This class of molecules are responsible for immune function, reproductive growth, and cellular signaling and differentiation[33,34]. Vitamin A is essential for the differentiation of epithelial cells into specialized tissues (mucus-secreting and pancreatic cells), playing a crucial role in the normal formation and maintenance of organs such as the lungs, heart, and eye[33-35]. It is also critical for vision, as it serves as an essential component of rhodopsin, the light-sensitive protein found in the rod cells of the retina that plays a pivotal role in the process of visual transduction[36,37].

Dietary vitamin A can be found in animal products, including kidney, liver, dairy products, and eggs[38]. They additionally can be seen as provitamin A (β-carotene) in plant sources, such as fruits and leafy vegetables[38,39]. Patients with vitamin A deficiency may present clinically with reduced night vision, dry eyes, keratomalacia, hyperkeratotic papular lesions, immunosuppression with recurrent infections, and dry skin[38-41]. Ophthalmological examination reveals conjunctival lesions with triangular perilimbal debris[41,42]. In healthy adults, vitamin A's recommended dietary allowance (RDA) is 700 mcg per day for women and 900 mcg per day for men. In pregnant women, the RDA is 770 mcg per day, while in children, it ranges between 300 to 900 mcg per day.

Toxicity: Excessive consumption of vitamin A can lead to acute and chronic toxicity[43]. This is characterized by elevated levels of > 80 mcg/dL in the body, known as hypervitaminosis A[43,44]. Acute vitamin A toxicity leads to nausea, vomiting, and elevated intracranial pressure, which can present clinically with blurred vision and vertigo[45]. Patients with chronic toxicity, in contrast, present clinically with alopecia, xerosis cutis, idiopathic intracranial hypertension, and hepatomegaly/hepatoxicity[45,46].

Vitamin D

Vitamin D is a fat-soluble entity that plays a vital role in calcium regulation and bone metabolism[47]. It has also been shown to play a key part in muscle, cardiovascular, immune, and nervous system functions[47-49]. Vitamin D is known as an immunomodulatory hormone, as experimental studies have shown that the active form [1,25-dihydroxyvitamin D_3 = 1,25(OH)2 D_3] exerts immunological activities on components of the adaptive and innate immune system[50]. There have been observed associations between low levels of serum 25-hydroxyvitamin D [25(OH)D] and the development of autoimmune disorders such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and others[51].

Vitamin D is obtained primarily from diet in the form of fish, milk, plants, fungi, and yeast [ergocalciferol (D_2) and cholecalciferol (D_3)][52]. Cholecalciferol can additionally be synthesized from skin exposure to the sun[53]. Both forms are converted to the storage form [25(OH)D] of vitamin D in the liver and then subsequently to the active form, 1,25(OH)2 D_3 (calcitriol) in the kidney that increases intestinal absorption of calcium, promotes bone resorption, and decreases renal excretion of calcium and phosphate (Figure 1)[54,55]. Deficiency of vitamin D can be caused by malabsorption, reduced sun exposure, chronic kidney disease, poor diet, and advanced liver disease[56]. In children, deficiency can lead to rickets, a condition characterized by a defect in mineralization of the epiphyseal plates, which can present clinically with craniotabes, rickety rosary, spinal column deformity, genu varum, and other musculoskeletal findings (*i.e.*, bone softening, gait disturbance, and growth retardation)[57,58]. In adults, it may lead to osteomalacia, characterized by abnormal bone mineralization, which may present clinically with bone pain, muscle weakness, and hypocalcemic tetany [59].

Recommendations regarding daily vitamin D intake vary by age. The Endocrine Society defines vitamin D [25(OH)D] deficiency as less than 30 ng/mL[60]. To maintain levels within the preferred range of 40 to 60 ng/mL, the organization recommends an intake of 400 to 1000 international units (IU) daily for infants below 1 year old, 600 to 1000 IU per day for children and adolescents up to 18 years old, and 1500 to 2000 IU for all adults. Oral vitamin D should be given to breastfed infants[61]. Darker skin and prematurity notably predispose to deficiency[62].

Toxicity: Elevated levels of vitamin D, also known as hypervitaminosis D, are related to excessive long-term intake, disruptions in the metabolic pathway, or concurrent disease that produces the active vitamin D metabolite[63]. This condition presents a range of clinical symptoms[63]. These include abdominal pain, polyuria, polydipsia, confusion, apathy, and loss of appetite[32,63]. Laboratory assessment typically shows hypercalcemia, hypercalciuria, and 25(OH)D concentrations > 150 ng/mL (> 375 nmol/L)[32,63,64]. Hypervitaminosis D can also be seen in granulomatous diseases that increase vitamin D levels by activating epithelioid macrophages[65].

Vitamin E

Vitamin E is the combined name for a group of fat-soluble vitamins with distinct antioxidant properties[66]. They act as antioxidants that protect red blood cells (RBCs) and neuronal membranes from free radical damage[66,67]. Naturally occurring vitamin E exists in several chemical forms that possess different levels of biological activity[68]. The α-tocopherol is the only form recognized to meet human metabolic needs[69]. Vitamin E is found in avocadoes, soybeans, nuts, olive oil, and leafy vegetables[68,69].

Clinical manifestations of Vitamin E deficiency include acanthocytosis, muscle weakness, ataxia, decreased proprioception and vibration, and hemolytic anemia[70]. Demyelination of the spinocerebellar tract and the posterior columns is responsible for ataxia and loss of proprioception and vibration, respectively[71,72]. These neurological symptoms may appear similar to those of patients with vitamin B_{12} deficiency. However, megaloblastic anemia and elevated serum

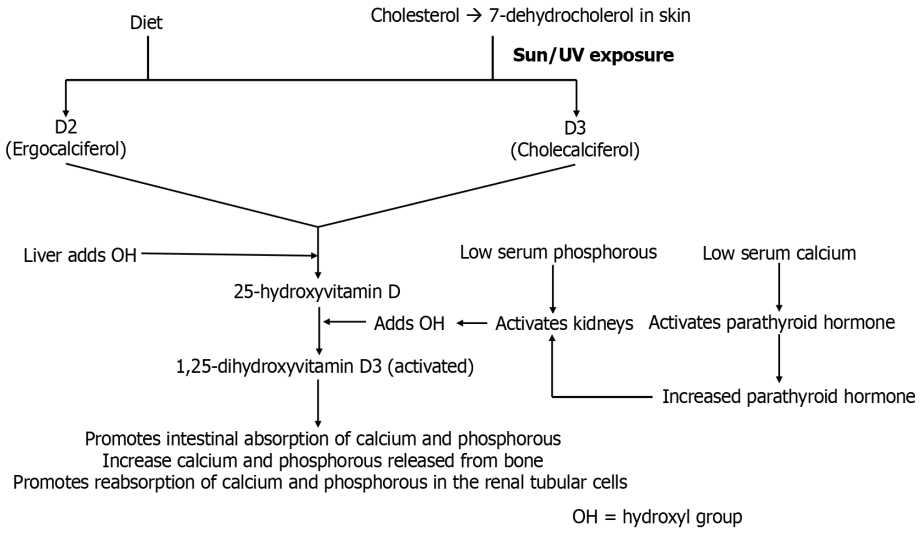


Figure 1 Diagram depicting the activation of vitamin D. Vitamin D from diet and the skin forms pre-vitamin D_3, which is converted to the storage form of vitamin D (25-hydroxyvitamin D) in the liver *via* 25-hydroxylase. Low serum calcium and phosphorous concentrations activate the kidney, converting 25(OH)D to activated 1,25(OH)2 D_3 *via* 1α-hydroxylase. This activated form subsequently promotes calcium and phosphorus reabsorption in the kidneys and intestines and increases the release of both minerals from the bone.

methylmalonic acid levels are absent[69-72]. The RDA for patients aged 14 years and older is 15 mg of α-tocopherol.

Toxicity: Vitamin E toxicity is associated with an elevated bleeding risk[73]. High-dose supplementation is known to alter the metabolism of vitamin K, which can enhance the anticoagulation effect in patients on warfarin[74]. In infants, toxicity is associated with the risk of enterocolitis[75].

Vitamin K

Vitamin K is a group of molecules, including phylloquinone (vitamin K_1) and a series of menaquinones (vitamin K_2), that are naturally present in some foods[76]. Menaquinones are designated as MK-4 through MK-13 based on the length of their unsaturated isoprenyl side chains, with MK-4, MK-7, and MK-9 being the most well-studied menaquinones[77]. Phylloquinone is found in green leafy vegetables and is the primary dietary source of vitamin K[78]. Menaquinone is primarily synthesized in the human gut by bacteria[77,79]. Vitamin K is activated by epoxide reductase to the reduced form, which serves as a cofactor for the γ-carboxylation of glutamic acid residues, that is essential for the maturation of clotting factors II, VII, IX, X, protein C and S[77-81].

Clinical manifestations of vitamin K deficiency include neonatal hemorrhage, as neonates possess sterile intestines and are unable to synthesize vitamin K[82]. Labs commonly show elevated prothrombin, activated partial thromboplastin, and normal bleeding time[82,83]. The absence of vitamin K in the human body can result in a range of complications, including impaired bone development, bleeding disorders, and elevated risk for cardiovascular disease[82-85]. For adult men and women, the RDA of vitamin K is 120 and 90 mcg per day, respectively.

SOURCES AND CLINICAL MANIFESTATIONS OF WATER-SOLUBLE VITAMIN DEFICIENCIES/EXCESS

Water-soluble vitamins are a group of organic compounds that are required in small amounts by the human body to prevent disorders of metabolism[86]. Given their chemical properties, regular intake is required to avoid nutritional deficiency. The water-soluble vitamins include vitamin C and vitamin B complex (thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, cobalamin, and ascorbic acid). These vitamins are readily excreted from the body except cobalamin (B_{12}) and folate (B_9)[87]. B_{12} is stored in the liver for approximately 3-4 years, while B_9 is stored in the same organ for 3-4 months[88]. B-complex deficiencies often result in dermatitis, glossitis, and diarrhea[88,89]. These compounds can also be coenzymes (*i.e.*, ascorbic acid) or precursors to coenzymes [*i.e.*, flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide+ (NAD+)][88-90]. The clinical manifestations of water-soluble vitamin deficiencies and their dietary sources can be seen below.

B_1 (thiamine)

Vitamin B_1, or thiamine, is a water-soluble compound that is a cofactor for various enzymes important in energy metabolism and glucose breakdown[91]. As such, it plays a critical role in cell growth, development, and function[91,92]. Approximately 80% of thiamin in the adult human body is thiamine pyrophosphate, the main metabolically active form of thiamine[91-93]. It can be found in nuts, poultry, soybeans, fortified foods, and peas[92-94]. Thiamine status is often measured indirectly by assaying transketolase activity following B_1 administration[95]. An increase in RBC transketolase activity following thiamine administration suggests deficiency[93-95].

Inadequate levels of thiamine results in impaired glucose breakdown, which leads to adenosine triphosphate (ATP) depletion[91-94]. As such, highly aerobic tissues (*i.e.*, the heart and brain) are affected more acutely[91-95]. Risk factors for deficiency include malnutrition and chronic alcohol overuse[96]. Insufficient levels of this vitamin can lead to several notable disorders, including Wernicke encephalopathy, Korsakoff syndrome, Wernicke-Korsakoff syndrome, and dry and wet beriberi[91-96].

Wernicke encephalopathy is an acute reversible life-threatening neurological condition due to B_1 deficiency in the setting of alcohol use that may present clinically with confusion, ophthalmoplegia/nystagmus, and ataxia[97]. Thiamine deficiency can also lead to Korsakoff syndrome, which is an amnestic disorder due to chronic alcohol use that presents clinically with confabulations, memory loss, and personality changes[97,98]. Wernicke-Korsakoff syndrome appears clinically as a combination of both disorders due to damage to the mammillary bodies and the medial dorsal nucleus of the thalamus[99]. Inadequate thiamine levels can also cause dry beriberi syndrome, which presents clinically with polyneuropathy and symmetric muscle wasting, as well as wet beriberi, which causes high-output heart failure due to systemic vasodilation[100,101]. The RDA for adult males and females is 1.2 and 1.0 mg per day, respectively.

B_2 (riboflavin)

Riboflavin is a water-soluble vitamin that serves as an essential component of two major coenzymes, FAD and flavin mononucleotide[102,103]. These enzymes play a significant part in energy production, cellular function, and growth[102-104]. FAD and flavin mononucleotide are used as cofactors in redox reactions (*i.e.*, succinate dehydrogenase reaction in the Krebs cycle)[105]. Riboflavin also plays a role as an antioxidant, as it helps in the regeneration of glutathione[106]. It can be found in fortified grains, dairy products, and certain fruits and vegetables[102-106].

Riboflavin deficiency can cause cheilosis and corneal vascularization. The RDA for women and men is 0.9 to 1.1 and 1.1 to 1.3 mg per day, respectively.

B_3 (niacin)

Niacin is a water-soluble B vitamin that is naturally present in many foods[107]. Body tissues convert niacin to its metabolically active form, NAD, which serves as a catalyst for more than 400 enzymes in the body[107]. NAD is also converted into another active form, nicotinamide adenine dinucleotide phosphate (NADP), which facilitates reactions in all tissues except skeletal muscle[108]. NAD is primarily involved in catabolic reactions that transform potential energy in proteins, fats, and carbohydrates to ATP[109]. NADP, in contrast, facilitates anabolic reactions such as fatty acid and cholesterol synthesis and plays a role in maintaining cellular antioxidant function[110]. Both are used in redox reactions and are cofactors for many dehydrogenases[107-110]. Niacin can be found in milk, meat, legumes, and fish[108,109]. Tryptophan is also a precursor for niacin to create NAD, so tryptophan is considered a dietary source of niacin[111].

Deficiencies are more common in developing countries due to insufficient dietary intake[108-112]. The lack of niacin and its precursor tryptophan leads to the manifestation of pellagra, which may be due to inadequate intake, Hartnup disease, malignant carcinoid syndrome, or isoniazid deficiency[113-115]. Symptoms of niacin deficiency include diarrhea, dementia (also hallucinations), and dermatitis (C3/C4 dermatome circumferential rash and hyperpigmentation on sun-exposed limbs)[108,110,113,115]. Hartnup disease is a rare autosomal recessive disorder due to a deficiency of neutral amino acid transporters in the proximal renal tubular cells and enterocytes[116]. This leads to neutral aminoaciduria and decreased absorption from the gut, resulting in little or no tryptophan for conversion to niacin, ultimately leading to pellagra-like symptoms. The RDA of niacin is 14 mg per day for women and 16 mg per day for men.

Toxicity: If niacin is consumed at high doses through supplements, it can lead to niacin toxicity. High doses of nicotinic acid may present clinically with facial flushing, hyperglycemia, hepatotoxicity, and hyperuricemia[117].

B_5 (pantothenic acid)

Pantothenic acid is a water-soluble compound that is naturally present in some foods and available as a dietary supplement[118]. The main function of vitamin B_5 is in the synthesis of coenzyme A (CoA) and acyl carrier protein[118,119]. It also serves as a component of fatty acid synthase[119]. Pantothenic acid is found in milk, vegetables, eggs, chicken, and others[118-120].

Deficiency of B_5 may lead to dermatitis, enteritis, alopecia, and adrenal insufficiency, which may lead to burning feet syndrome, distal paresthesias, and dysesthesia[119-121]. The RDA for adult men and women is 5 mg per day.

B_6 (pyridoxine)

Pyridoxine is a group of water-soluble vitamins that are naturally present in many foods[122]. Pyridoxal 5′ phosphate and pyridoxamine 5′ phosphate are the active coenzyme forms of B_6[123]. Pyridoxal 5′ phosphate is a cofactor that is used in several metabolic processes, including transamination, decarboxylation, and phosphorylation reactions[124]. It also plays a vital role in protein, carbohydrate, lipid metabolism, and the creation of RBCs[122-124]. Pyridoxine can be found in liver, poultry, and fortified cereals[122,123].

Patients with pyridoxine deficiency may present clinically with convulsions, hyperirritability, and peripheral neuropathy[125]. Some patients may appear with sideroblastic anemia due to impaired hemoglobin synthesis and iron excess[126]. The RDA for adults is 1.75 mg per day.

B_7 (biotin)

Biotin is a water-soluble compound that plays a role in energy metabolism and the regulation of oxidative stress[127]. It serves as a cofactor for several carboxylation enzymes, including pyruvate carboxylase, acetyl-CoA carboxylase, and

propionyl-CoA carboxylase[127,128]. The vitamin can be found in many foods, such as egg yolk, liver, wheat, dairy, rice, and spinach[127,128].

Biotin deficiency is relatively rare[129]. It is commonly caused by long-term antibiotic use or excessive ingestion of raw egg whites, as raw egg whites contain a large volume of avidin, which binds to biotin[129,130]. Patients with a deficiency in this vitamin may clinically present with dermatitis, enteritis, and alopecia[127-130]. Intake recommendations range between 5 and 35 mcg per day.

B_9 (Folate)

Folate is a water-soluble B molecule that is present in multiple foods and is available as a dietary supplement[131]. Folate in foods is in the tetrahydrofolate form and usually possesses additional glutamate residues, making them polyglutamates[131,132]. Folic acid is the completely oxidized monoglutamate form of the vitamin that is used in most dietary supplements and fortified foods[133]. Folate plays a crucial role in the methylation/1-carbon transfer reactions necessary for deoxyribonucleic acid (DNA) and ribonucleic acid synthesis and metabolism of amino acids[131-133]. One of the most important folate-dependent reactions is the methylation of deoxyuridylate to thymidylate in the formation of DNA, which is required for proper cell division[134]. Impairment in this reaction initiates several steps that can lead to megaloblastic anemia, one of the hallmarks of folate deficiency[135]. Folate can be found in leafy green vegetables, eggs, and milk[132-136]. It is also produced by the guy microbiota, and a small, reserved pool is stored primarily in the liver [131-135].

Risk factors for folate deficiency include pregnancy, chronic alcohol use, digestive disorders such as Crohn's disease, and several medications (*i.e.*, phenytoin, trimethoprim, and methotrexate)[131,136,137]. These patients may clinically present with glossitis, megaloblastic anemia, and oral ulcers[134-137]. Folate deficiency before and during pregnancy increases the risk of neural tube defects[138]. A healthy adult requires 400 mcg per day, with higher intakes recommended during pregnancy to prevent neural tube defects.

B_{12} (cobalamin)

Vitamin B_{12} is a water-soluble vitamin that is required for the development, myelination, and function of the central nervous system[139]. Cobalamin is also essential for RBC formation and DNA synthesis[139,140]. It serves as a cofactor for methionine synthase and L-methylmalonyl-CoA mutase[141]. Methionine synthase catalyzes the conversion of homocysteine to methionine[142]. Methionine is needed for the creation of S-adenosylmethionine, which is a universal methyl donor for several substrates, including ribonucleic acid, DNA, proteins, and lipids[141,142]. L-methylmalonyl-CoA mutase converts L-methylmalonyl-CoA to succinyl-CoA in the metabolism of propionate. B_{12} is found in animal products (*i.e.*, meat, dairy, eggs) and is synthesized only by intestinal microbiota[141-143]. The site of synthesis in humans is distal to the site of absorption[144]. Thus, B_{12} must be consumed *via* animal products[143,144].

Humans possess a very large reserve pool of B_{12} that is primarily stored in the liver[145]. Deficiency can be caused by a lack of intrinsic factor (*i.e.*, pernicious anemia, gastric bypass surgery), malabsorption (*i.e.*, enteritis, sprue, achlorhydria, alcohol overuse, bacterial overgrowth, *Diphyllobothrium latum*), insufficient intake (*i.e.*, veganism), absence of ileum (surgical resection, *i.e.*, Crohn's) and certain medications (*i.e.*, metformin)[146-149]. Patients with deficiency may present with megaloblastic anemia, paresthesias, and subacute combined degeneration in severe cases (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin[141,143,144,148-150]. B_{12} deficiency is associated with elevated serum homocysteine and methylmalonic acid levels and secondary folate deficiency [146-151]. A prolonged state of insufficiency can lead to irreversible nerve damage. The RDA of cobalamin for adults is 2.4 mcg per day.

Vitamin C (ascorbic acid)

Vitamin C, also known as L-ascorbic acid, is a water-soluble vitamin that is present in certain foods[152]. Unlike most animals, humans cannot produce endogenous vitamin C, so it is essentially a dietary component[153]. Vitamin C is required for the biosynthesis of L-carnitine, collagen, and certain neurotransmitters[154]. It is necessary for the hydroxylation of lysine and proline in collagen synthesis, which plays a vital role in wound healing[152-154]. The vitamin is also necessary for dopamine β-hydroxylase, which converts dopamine to norepinephrine[155]. It additionally serves as an antioxidant and has been shown to regenerate other antioxidants within the body, including vitamin E[156,157]. In addition to its synthetic and antioxidant properties, vitamin C facilitates iron absorption and plays an important role in immune function[158]. It is primarily found in fruits and vegetables, such as citrus, potatoes, berries, and green leafy vegetables[155-159].

Severe vitamin C deficiency can result in scurvy, a disorder characterized by swollen gums, easy bruising, petechiae, anemia, hemarthrosis, poor wound healing, corkscrew hair, and perifollicular and subperiosteal hemorrhages[160]. This simultaneously results in a weakened immune system[160,161]. The recommended intake may vary based on age and gender but typically falls between 40 and 120 mg per day.

Toxicity: Excess vitamin C intake can lead to nausea, vomiting, fatigue, diarrhea, and calcium oxalate stones[162,163]. Elevated levels can also increase iron toxicity in predisposed individuals by increasing dietary iron absorption (*i.e.*, it can worsen transfusion-related iron overload or hemochromatosis)[164,165].

Table 1 Laboratory testing for diagnostic evaluation of several micronutrient deficiencies

Vitamin	Diagnostic test	Specimen type	Diagnostic values
A	Vitamin A (retinol) level	Serum	Low
D	Total 25-hydroxyvitamin D level	Serum	Low
E	Vitamin E (α-tocopherol) level	Serum	Low
K[1]	PT/INR	Serum	Prolonged/elevated
Thiamine[2]	Thiamine, whole blood	Whole blood EDTA	Low
Riboflavin	Riboflavin level or urinary excretion rate	Plasma or urine	Low
Niacin	Niacin level or urinary excretion of N1-methylnicotinamide	Serum or urine	Low
Pantothenic acid	Pantothenic acid level	Serum	Low
Pyridoxine[3]	Pyridoxal phosphate	Serum	Low
Biotin	Biotin level	Serum	Low
Folate	Vitamin B12 and folate levels	Serum	Low
Cobalamin[4]	Vitamin B12 and folate levels	Serum	Low
Ascorbic acid[5]	Ascorbic acid level	Serum	Low

[1]If phytonadione (Vitamin K1) 1 mg IV dramatically decreases PT within 2-6 hours, a liver disorder is unlikely, and the diagnosis of vitamin K deficiency is confirmed.
[2]This assay measures the concentration of the primary active form of vitamin B1 (thiamine diphosphate). Approximately 90 percent of B_1 present in whole blood is thiamine diphosphate. Thiamine monophosphate and thiamine, which comprise the remaining 10 percent, are not measured. Values less than 70-180 nmol/L are considered diagnostic for thiamine deficiency. The United States Food and Drug Administration has not cleared or approved it. The thiamine loading test, which measures erythrocyte transketolase in red blood cells, is still the best indicator for thiamine deficiency. However, the test is expensive and time-consuming.
[3]Diagnosis of pyridoxine deficiency is usually made clinically. There is no single acceptable laboratory testing to confirm diagnosis. However, serum pyridoxal phosphate is usually the most common.
[4]A complete blood count, in conjunction with B12 and folate levels, should be obtained to detect megaloblastic anemia. Folate levels should also be measured to differentiate B12 from folate deficiency as a cause of anemia, as folate supplementation may alleviate megaloblastic anemia but worsen neurologic deficits.
[5]Vitamin C deficiency is a clinical diagnosis based on risk factors and gingival or skin findings. Laboratory diagnosis requires the measurement of blood ascorbic values. < 0.2 mg/dL (< 11 mcmol/L) indicate vitamin C deficiency.
PT: Prothrombin time; INR: International normalized ratio; EDTA: Ethylenediaminetetraacetic acid.

DIAGNOSIS AND TREATMENT OF FAT/WATER-SOLUBLE VITAMIN DEFICIENCIES

Before treatment, a practitioner must obtain a diagnosis. This begins with attaining a good clinical history from the patient, including their surgical past and dietary habits. Based on clinical suspicion, the provider should perform a complete physical examination to look for the clinical signs described above. The next step includes a series of direct and indirect assays performed on the blood to determine vitamin levels, as seen in Table 1. Some deficiencies are clinically diagnosed, and laboratory assessment further confirms suspicion[166-168]. Biomarker limitations in a lab setting stem from elements such as cost, assay standardization, variability in measurement, and sampling handling. These host of factors can ultimately affect biomarker reliability and accuracy, especially in low-income countries that may not have adequate resources. Due to this fact, clinicians should not diagnose MND, or excess solely based on laboratory values.

Treatment of fat-soluble vitamin deficiencies

Treatment of fat-soluble vitamin deficiencies depends on multiple factors, including the severity, deficiency type, and the patient's individual needs (*i.e.*, pregnancy, growth, and underlying disease)[169]. The most common method for the treatment of fat-soluble vitamin deficiency is supplementation with specific preparations of vitamins A, D, E, or K[33,47,68,166,168,170]. These vitamins can be taken in the form of capsules, tablets, or drinkable preparations, but they can also be administered intravenously (IV) or intramuscularly (IM), depending on the severity of the deficiency[26-36,41-47,168]. There are a wide variety of therapeutic regimens that have been proposed by several academic societies (*i.e.*, internal medicine, endocrine, rheumatology, and others)[30,165-170]. It is important to emphasize that the suggested therapeutic regimens are mostly based on studies that do not meet evidence-based medicine criteria and are rather a combination of suggestions from multiple medical societies from mostly the United States and Europe (Table 2).

A multitude of studies have concluded that vitamin A supplementation reduces childhood morbidity and mortality, especially in patients with serum retinol concentrations less than 20 mcg/dL[171-173]. In regions with a high prevalence of vitamin A deficiency, the WHO recommends a one-time dose of 100000 IU in children 6 to 11 months, followed by 200,000 IU every 4 to 6 months up to age five[174,175]. For pregnant women who are at risk, the WHO recommends 10000

Table 2 Summary of medical therapy for several micronutrient deficiencies in adult patients

Vitamin	Clinical manifestations of deficiency	Recommended treatment
A	Nyctalopia, xerosis cutis, xeropthalmia, immunosuppression, keratomalacia, and conjunctival squamous metaplasia Bitot spots	Vitamin A palmitate 60000 IU (18000 mcg RAE) orally once per day for 2 days, followed by 4500 IU once a day
D	Bone pain, muscle weakness, depression, hair loss, and hypocalcemic tetany	Ergocalciferol (vitamin D2) 50000 IU orally every 7 days for 8 weeks
E	Hemolytic anemia, muscle weakness, ataxia, and decreased proprioception and vibration	α-tocopherol is 15 to 25 mg/kg orally once daily or 200 IU of mixed tocopherols daily. Injections should be used to treat neuropathy and patients with malabsorption syndromes
K	Increased risk for bleeding	Phytonadione 1 to 10 mg orally for nonemergent correction of prolonged INR in patients taking anticoagulants. When partial correction of INR is desirable (*i.e.*, prosthetic heart valve), 1 to 2.5 mg doses should be used
Thiamine	Wernicke encephalopathy: Confusion, ophthalmoplegia, nystagmus, and ataxia. Korsakoff syndrome: Confabulations, personality changes, and permanent memory loss. Wernicke-Korsakoff syndrome: Presentation is a combination of Wernicke and Korsakoff syndrome. Dry beriberi: Polyneuropathy and symmetric muscle wasting. Wet beriberi: High-output heart failure	IV thiamine 250-500 mg/day should be given for 3-5 days, followed by oral thiamine 250-300 mg/day for chronic alcoholics and other patients at risk for deficiency. Patients with suspected Wernicke receive 500 mg of thiamine diluted in 50-100 mL of normal saline infused over 30 minutes three times daily for three days, followed by 250 mg IV daily for 3 to 5 days or until clinical improvement. 100 mg IV once per day for several days in patients with edema and congestion due to cardiovascular beriberi
Riboflavin	Cheilosis and corneal vascularization	5 to 30 mg orally once per day until recovery. Other water-soluble vitamins should also be given
Niacin	Diarrhea, dermatitis, and dementia (also hallucinations)	Nicotinamide 250 to 500 mg orally once per day
Pantothenic acid	Enteritis, dermatitis, alopecia, and adrenal insufficiency may lead to "burning feet syndrome"	Pantothenic acid 5-10 mg orally once per day
Pyridoxine	Hyperirritability, peripheral neuropathy, convulsions, and sideroblastic anemia	Pyridoxine 50-100 mg orally once per day. Patients taking isoniazid should be given 30-50 mg orally once a day
Biotin	Isolated deficiency is relatively rare. Enteritis, dermatitis, and alopecia	Biotin 5-20 mg orally once per day
Folate	Megaloblastic anemia, glossitis, fatigue, and pale skin	Folic acid 400-1000 mcg orally once per day. Women who plan on becoming pregnant should be supplemented with 400 to 800 mcg once per day
Cobalamin	Megaloblastic anemia, paresthesias, depression/anxiety, pale skin, cognitive dysfunction, and SCD	Vitamin B12 1000-2000 mcg orally once per day in patients who are significantly deficient or possess neurologic symptoms. For severe deficiency, 1 mg IM 1-4 times per week for several weeks until anemia and symptoms resolve
Ascorbic acid	Scurvy-swollen gums, petechiae, anemia, poor wound healing, hemarthrosis, "corkscrew" hair, and perifollicular and subperiosteal hemorrhages	For scurvy, use 500-1000 mg orally once per day for 1-2 weeks until symptoms and signs resolve

IU: International units; RAE: Retinol activity equivalents; INR: International normalized ratio; IV: Intravenous; SCD: Subacute combined degeneration; IM: Intramuscular.

IU daily or 25,000 IU weekly for 12 weeks[176]. There are currently no international guidelines for the treatment of asymptomatic vitamin A deficiency for adults in resource-rich regions.

The most cost-effective method of replenishing 25(OH)D levels in patients with vitamin D deficiency is oral ergocalciferol at 50000 IU per week for eight weeks[177]. The optimal time for rechecking vitamin D stores after therapy is not defined, but the goal is to achieve at least a minimum of 30 ng/mL[177,178]. Serum 25(OH)D levels should be obtained again after completion of therapy, and if values have not reached or surpassed the minimum, a second eight-week course should be prescribed. If the target goal is still not achieved, the most likely cause is nonadherence or malabsorption. Patients with suspected malabsorption should be referred to a gastroenterologist for further evaluation. Once levels are replete, vitamin D should be instituted at 800 to 2000 IU daily from supplemental and dietary sources[177-179].

Vitamin E deficiency is extremely rare in humans and is mainly caused by irregularities in dietary fat absorption or metabolism[180]. A supplementation of 15 to 25 mg/kg/day or 200 IU of tocopherols can be used in patients who are deficient[180-182]. IM or subcutaneous injection can be used in patients who have oral ingestion and/or intestinal issues. The treatment of vitamin K deficiency is limited to neonates and anticoagulation overdoses (*i.e.*, warfarin)[183-185].

Treatment of water-soluble vitamin deficiencies

The treatment of thiamine deficiency is based on the severity and the clinical presentation of the patient. In patients at high risk for thiamine deficiency, such as chronic alcoholics, IV thiamine 250-500 mg/day should be given for 3-5 days, followed by oral thiamine 250-300 mg/day[186,187]. Patients with suspected Wernicke encephalopathy should receive 500 mg of thiamine diluted in 50-100 mL of normal saline infused over 30 minutes three times daily for 3 days, followed

by 250 mg IV daily for 3 to 5 days or until clinical improvement[188,189].

Vitamin B_{12} deficiency can be treated with oral therapy or IM injections of cyanocobalamin[190,191]. More than 8% of the standard injectable dose of 1 mg is absorbed, which allows for swift replacement in patients with severe neurologic symptoms or deficiency[190-192]. Guidelines from the British Society for Hematology recommend IM injections three times per week for two weeks in patients without neurologic deficits and every other day for up to three weeks or until improvement in patients with deficits[191]. In general, patients with irreversible causes of B_{12} deficiency should remain on lifelong therapy, whereas those with reversible causes should be treated until the deficiency is corrected or until symptoms resolve[193,194]. Oral high-dose B_{12} (1-2 mg daily) is equally effective to IM for correcting neurologic symptoms and anemia in patients with no contraindications to oral therapy[193-195].

Folate levels below two ng/mL are generally considered deficient[196,197]. All patients with folate deficiency should receive supplemental folic acid for treatment[198,199]. Oral folic acid (1-5 mg/day) typically suffice for management[198-200]. Other forms of therapy, including IV, IM, or subcutaneous, can be used in patients who are intolerant to oral medications. The duration of treatment is based on whether the cause of the initial deficiency persists. Patients with short gut or malabsorption syndromes typically require long-term management[196,198,199,201]. It is essential to obtain B_{12} levels in patients who are folate deficient as folic acid supplementation may correct the anemia but worsen the neurological signs and symptoms of B_{12} deficiency if present[202,203].

CONCLUSION

In summary, micronutrients are essential to sustain life, and nutrition is a modifiable risk factor that can be targeted to optimize health and well-being. Nutritional deficiencies can often lead to loss of bodily functions, developmental failure, and other medical conditions, including vision loss and lack of immunity. The major causes of nutritional deficiencies are insufficient food intake, malabsorption, and consumption of diets lacking essential nutrients. MNDs are the most prevalent type of nutritional deficiency and are a leading cause of worldwide morbidity and mortality. Deficiency in either fat or water-soluble vitamins can lead to serious conditions such as vision loss, pellagra, beriberi, recurrent infections, and decreased cognitive function, among others. Developing countries are most susceptible to these deficiencies, and diagnosis starts with a good clinical history and physical examination. Prompt recognition and treatment can drastically reduce morbidity and mortality, especially in developing countries.

FOOTNOTES

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MINIREVIEWS

Challenges and solutions in the treatment of spinal disorders in patients with skeletal dysplasia: A comprehensive review

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Abstract

Skeletal dysplasia includes numerous genetic disorders marked by abnormal bone and cartilage growth, causing various spinal issues. The 2023 nosology identifies 771 distinct dysplasias involving 552 genes, with achondroplasia being the most common and significantly affecting the spine. Other disorders include type II collagenopathies, sulphation defects, Filamin B disorders, and osteogenesis imperfecta, presenting with short stature, limb deformities, joint contractures, and spinal abnormalities. Spinal pathology often impacts physeal growth areas, leading to conditions like foramen magnum stenosis, atlantoaxial instability, spinal stenosis, kyphosis, and scoliosis. Non-orthopaedic symptoms can include hearing and vision loss, neurological issues like hydrocephalus, and cardiac abnormalities. The incidence is around 1 in 4000 to 5000 births, with achondroplasia at about 1 in 30000 live births. Advances in genetics and imaging enable prenatal diagnosis, though milder cases may go undetected. Effective management requires a multidisciplinary approach involving various specialists. This review emphasises early diagnosis, continuous monitoring, and comprehensive management of spinal pathology in skeletal dysplasia. In the current article, the authors present a thorough review on spinal conditions associated with skeletal dysplasia, their pathophysiology and management options.

Key Words: Skeletal dysplasia; Spinal disorders; Achondroplasia; Spondyloepiphyseal dysplasia; Mucopolysccharidosis; Osteogenesis imperfecta

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Core Tip: Spinal disorders are commonly encountered in patients with skeletal dysplasia. Skeletal dysplasias often impacts physeal growth areas, leading to conditions like foramen magnum stenosis, atlantoaxial instability, spinal stenosis, kyphosis, and scoliosis. The current article provides a detailed review of the various types of skeletal dysplasia and its associated spectrum of spinal disorders, along with common clinical presentation and management options and outcomes as described in literature.

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INTRODUCTION

Skeletal dysplasia encompasses a diverse group of genetic disorders defined by atypical bone or cartilage growth and development, resulting in various spinal manifestations[1]. The 2023 nosology of skeletal disorders comprises 771 diseases with 552 genes classified into 41 groups based on their clinical, radiographic, and/or molecular phenotypes[2].

Among these, the most prevalent is achondroplasia, which belongs to the fibroblast growth factor receptor 3 (FGFR3) chondrodysplasia group and is well-known for its spinal involvement[3]. Other disorders with significant spinal manifestations include type II collagen disorders, sulphation disorders, Filamin B disorders, the transient receptor potential vanilloid type 4 (TRPV4) group, pseudoachondroplasia, the bent bone dysplasia group, the chondrodysplasia punctata group, osteogenesis imperfecta (OI), and lysosomal storage diseases. These disorders result in a wide array of phenotypic manifestations, including disproportionate short stature, limb deformities, joint contractures, and significant spinal abnormalities. Spinal pathology often occurs where there is physeal growth, such as the skull base (foramen magnum), odontoid process, neuro-central synchondrosis, and vertebral endplates[2]. Disturbances in these growth areas can lead to conditions like foramen magnum stenosis (FMS), atlantoaxial instability, spinal stenosis, kyphosis, and scoliosis. Additionally, non-orthopaedic features such as hearing and vision loss, characteristic facial appearances, neurological issues like hydrocephalus, and cardiac and pulmonary abnormalities may also be present. The overall incidence of skeletal dysplasia is relatively uncommon, estimated at one in every 4000 to 5000 births, though this may be an underestimation as some disorders are not apparent at birth[4,5].

Traditionally, the diagnosis of skeletal dysplasia was based on family history, clinical observations, and radiographic findings. The key radiographs to aid diagnosis are an anteroposterior view of both lower extremities from hip to ankle and a lateral view of the spine. However, advances in molecular genetics and imaging techniques have made genetic testing routine, enabling prenatal diagnosis through molecular screening panels when ultrasonography raises concerns for skeletal dysplasia[4]. Despite these advancements, milder cases, late-onset phenotypes, or those without prenatal screening might go undetected at birth. Spinal disorders are a major cause of morbidity and mortality in skeletal dysplasia, often presenting early and progressively worsening. Spinal cord (SAC) compression, which can result in paralysis or death, is particularly concerning. Prevention of these severe outcomes requires early detection, close monitoring, and sometimes immediate surgical intervention. Unfortunately, spinal manifestations are frequently missed due to misdiagnosis or insufficient understanding of the disorders' natural progression.

Effective management requires a collaborative approach involving orthopaedic surgeons, neurologists, geneticists, and rehabilitation specialists to address the diverse and evolving spinal issues associated with skeletal dysplasia. By comprehending the specific spinal complications linked to various types of skeletal dysplasia, healthcare providers can devise more effective treatment strategies and improve long-term outcomes for affected individuals.

This review aims to provide a general overview of spinal manifestations in various skeletal dysplasias (Table 1) with an emphasis on early diagnosis, continuous monitoring, and management of spinal pathology.

LITERATURE REVIEWS

This review was conducted following established guidelines for systematic literature reviews. A comprehensive search was performed in PubMed, Scopus, and Web of Science databases using the following keywords: (1) Skeletal dysplasia; (2) Spinal disorders; (3) Achondroplasia; (4) Spondyloepiphyseal dysplasia; and (5) Mucopolysaccharidosis. Articles published between 2000 and 2024 were included, with a preference for high-quality studies, clinical trials, and systematic reviews. The inclusion criteria were studies reporting spinal manifestations, treatment outcomes, and management strategies in skeletal dysplasia. Exclusion criteria included non-English articles, and studies without spinal focus. Data extraction was performed independently by two authors, with disagreements resolved through discussion.

DISCUSSION

FGFR3 related disorders

FGFR3 disorders comprise a spectrum of disorders that include achondroplasia, thanatophoric dysplasia, and hypochondroplasia. They are all inherited as autosomal dominant disorders due to heterozygosity for mutations in FGFR3 (4p16.3) [5]. All three disorders are osteochondrodysplasias characterized by varying degrees of skeletal abnormalities. Achondroplasia is nonlethal with some rare exceptions. Hypochondroplasia can phenotypically mimic achondroplasia but is usually milder. Thanatophoric dysplasia is lethal without very aggressive interventions[6].

Achondroplasia

Achondroplasia is the most common hereditary skeletal dysplasia requiring treatment of the spinal disorder. It follows either an autosomal dominant pattern of inheritance with 100% penetrance or a sporadic mutation. Achondroplasia occurs in approximately 1:20000 to 1:30000 live births per year[7,8]. The homozygous form is lethal resulting in stillbirth, while advanced paternal age has been related to sporadic cases[9].

Pathophysiology: Achondroplasia is typically characterized by rhizomelic (proximal) limb shortening, protuberant abdomen, macrocephaly, hypotonia, frontal bossing, and midface hypoplasia[9]. There is a decrease in endochondral ossification caused by activating mutation of FGFR3 in its transmembrane domain. Bones formed due to membranous ossification (skull vault, clavicle, and pelvis) are unaffected.

Spinal manifestations of achondroplasia include the following: (1) Foramen magnum stenosis and short clivus; (2) Craniocervical spinal canal stenosis resulting in cervicomedullary compression; (3) Posterior vertebral scalloping; (4) Thoracic spine stenosis; (5) Thoracolumbar kyphosis and lumbar hyperlordosis; and (6) Reduced pedicle length and interpedicular distance particularly in the lumbar spine causing spinal stenosis[9-12].

At birth, an infant with achondroplasia has hypotonia in the trunk and the extremities. The cause of hypotonia remains unclear regarding whether it is the result of partial neurological deficit secondary to FMS[12]. There is an increased frequency of sleep apnea in these infants, sometimes leading to sudden death. Sleep apnea monitors are often used for the first several months in many of these infants, and if sleep apnea is found clinically significant, evaluation for FMS is needed as there may be underlying cord compression[13]. Although atlantoaxial instability is commonly seen in other skeletal dysplasias, it is rarely seen in achondroplasia[14,15].

Management: FMS is a serious and potentially life-threatening complication in achondroplasia patients. Almost all infants with achondroplasia have a foramen magnum size less than 3 SD below the mean[15]. Infants and younger children are at greater risk of developing FMS. FMS can lead to cervicomedullary compression, resulting in sleep apnea and sudden death in infants. Mortality rate as high as 7.5% has been reported in the literature[16]. As per the European Achondroplasia Forum, all infants should be monitored clinically for FMS every 3-4 months from birth to the age of 1 year, thereafter every 3-6 months until the age of 3 years. After the age of 3 years, monitoring for FMS should be based on individual needs and local protocols. Magnetic resonance imaging (MRI) should be undertaken as routine monitoring for FMS at 3-6 months of age and repeated according to findings in other routine assessments[17].

The best approach to treatment and who should receive it remains unclear. One study of 32 children with achondroplasia found that 28% had sleep apnea, and 22% had abnormal sleep study results. Both conditions improved in the 6 children who underwent foramen magnum decompression[18]. It has been noted that combining foramen magnum decompression with external ventricular drainage can enhance safety and effectiveness by addressing abnormal cerebrospinal fluid (CSF) flow[19-21]. Symptoms like ataxia, incontinence, and breathing difficulties have been successfully treated with foramen magnum decompression and atlas laminectomy in patients ranging from 7 months to 30 years old. Some experts suggest performing cervicomedullary decompression in asymptomatic children if SAC changes appear on T2-weighted MRI[22,23]. However, it is rarely necessary to perform foramen magnum decompression in older children or adults[24].

In the cervical spine below the foramen magnum in achondroplasia, the principal disorder is diffuse spinal stenosis. Although a small spinal canal is present at birth, signs and symptoms of neural compression in the subaxial cervical spine are commonly not seen until middle age or later. The reason behind this may be the presence of degenerative changes in an already compromised spinal canal[25]. The clinical features could range from mild pain and sensory changes in the upper extremities to cervical myelopathy. If the motor deficit in the upper or lower extremities is present, laminectomy at multiple levels may be needed. MRI defines the level of compression, which is usually multiple. Laminectomy is the mainstay of treatment but this leads to instability and progressive deformity requiring complex fixation. To mitigate this risk, Afshari *et al*[26] developed a novel modified augmented laminoplasty that increases spinal canal diameter while preserving the posterior column stability. The study showed promising outcomes in terms of improvement of symptoms and prevention of deformity, suggesting augmented laminoplasty as a viable alternative to fixation.

Thoracolumbar kyphosis: When an infant begins to sit upright, features such as a large head, flat chest, protuberant abdomen, and trunk hypotonia can highlight thoracolumbar kyphosis (TLK), which is a condition that is frequently observed in newborns. When the child lies prone, the apparent deformity might get better. On X-rays, T12 and L1 apical wedging is commonly observed, usually affecting vertebrae from T10 to L4. TLK frequency peaks at 87% in the first two years of life and falls to 11% in the fifth and tenth years. Apical vertebral translation (5% of cases) and apical vertebral wedging (6%) are radiographic indicators of persistent TLK. Unresolved TLK is also linked to developmental motor delay.

Patients with kyphotic curves between 20 degrees and 40 degrees should be monitored for progressive deformity and symptoms of SAC compression. As the child begins to stand and walk, lumbosacral hyperlordosis may become apparent, likely due to excessive anterior pelvic tilt while standing. Management of TLK in achondroplasia involves a combination of monitoring, physical therapy, and, in severe cases, surgical intervention. Early detection is crucial, especially since TLK can be resolved as children grow. Regular radiographic assessments help track progression. Physical therapy aims to strengthen trunk muscles, improving posture and stability. Surgical management of TLK in achondroplasia is considered when conservative measures fail or if there is significant progression of the deformity, neurological compromise, or severe pain. The primary goals of surgery are to stabilize the spine, correct the deformity, and prevent further neurological deterioration. Surgical techniques include spinal arthrodesis and instrumentation[27]. The authors have summarized the studies describing surgical management in achondroplasia in Table 2[28-32].

During in utero spine development, impaired longitudinal growth of the posterior arches occurs, resulting in premature fusion of pedicles with vertebral bodies leading to shortened pedicles, and reduced cross sectional area of spinal canal leaving less space available for neural elements[33]. Neurologic issues from spinal stenosis are the primary concern for adolescents and adults with achondroplasia, often presenting as back pain, claudication, and bladder incontinence[34]. Laminectomy with fusion is a commonly performed surgical intervention. Surgical decompression for spinal stenosis in achondroplasia patients typically results in good symptom relief and functional improvement, particularly if done within six months of symptom onset. However, significant risks, including complications, recurrence of stenosis, and spinal destabilisation, must be managed. Thinning of the dura after extensive laminectomy can cause pseudomeningoceles, leading to neurological problems or pain. In skeletally immature patients, instrumented stabilization may be more effective than decompression alone to prevent spinal deformity[35].

In cases of lumbar stenosis with TLK, both contribute to neurological symptoms, requiring MRI to assess all compression levels[36,37]. For lumbar stenosis with anterior SAC compression at the kyphosis apex, anterior decompression and fusion, along with posterior multilevel laminectomy and instrumented fusion, is recommended. Anterior decompression may be done *via* vertebrectomy and bone graft fusion or through the pedicles using cages and bone grafts. Pedicle screws and rods are placed during posterior decompression, followed by bone graft fusion[28,29,35].

Thanatophoric dysplasia

It is another condition linked to FGFR3 mutations, is usually lethal in the perinatal period. Respiratory insufficiency typically results in early neonatal death and is due to a small chest cavity and/or foramen magnum narrowing with brain stem compression[38,39]. However, long-term survivors have been reported, including rare reports of survival to adulthood with aggressive ventilatory support and surgical management of neurologic complications. Other spinal manifestations include a cloverleaf skull, platyspondyly, and generalized hypotonia[40].

Hypochondroplasia

A milder form of skeletal dysplasia compared to achondroplasia and caused by *FGFR3* gene mutations, often results in lumbar spinal stenosis and mild kyphosis[41]. Patients may develop neurogenic claudication and back pain due to stenosis, while mild kyphosis in the thoracolumbar region generally causes less severe issues. Shortened pedicles contribute to the development of lumbar stenosis, often requiring surgical decompression. Compared to achondroplasia, hypochondroplasia presents with less pronounced skeletal abnormalities, but careful monitoring and intervention are still necessary[9,24].

Solute carrier 26A related disorder

Diastrophic dysplasia: Diastrophic dysplasia is a rare genetic disorder characterized by distinctive clinical features that typically allow for diagnosis at birth. The incidence is approximately 1 in 1 million in most countries, but Finland reports a significantly higher number of cases, contributing to much of the current literature on the condition. The disorder is linked to a genetic defect in diastrophic dysplasia sulfate transportase, located on chromosome 5q31-q34[42].

Pathophysiology: The pathophysiology of diastrophic dysplasia is rooted in a genetic defect affecting sulfate transport, leading to abnormal cartilage and bone development. Key diagnostic features include micromelia (markedly short stature), "hitchhiker's thumb", stiff proximal interphalangeal joints of the fingers, severe equinovarus foot deformity, and the development of external ear cysts within weeks of birth, resulting in the characteristic "cauliflower ear". The spine is notably affected, with all patients exhibiting spina bifida of the cervical spine, though this does not typically cause symptoms. The most significant spinal issue is mid-cervical kyphosis, which, if progressive, can lead to severe deformity and SAC compression[43,44].

Clinical features: Patients with diastrophic dysplasia display a range of clinical features, including short stature, joint stiffness, and various skeletal deformities. Approximately 25% of affected individuals have a cleft palate. Spinal abnormalities are common, with mild cervical kyphosis often resolving by age 7, but in some cases, progressive kyphosis leads to severe spinal deformity. Kyphoscoliosis is the primary spinal disorder in the thoracic region, with varying degrees of severity. Severe thoracic kyphoscoliosis can cause significant physical issues, such as swallowing difficulties, though neurologic symptoms are rare.

Management: Management of diastrophic dysplasia focuses on early detection and treatment of spinal deformities to prevent progression to severe kyphosis or scoliosis. In cases of progressive cervical kyphosis, cervical fusion is recommended to stabilize the spine and prevent SAC compression. For thoracic kyphoscoliosis, treatment may include the use of a brace or, in more severe cases, anterior and posterior spinal fusion with instrumentation. Monitoring and

Table 1 Spinal disorders associated with skeletal dysplasia

Group/name of disorder	Inheritance	Gene	Case-control studies	Cohort studies	Hydroxy	Choline kinase	Atlantoaxial instability	Basilar invagination	Chronic viral B-hepatitis	Thoracolumbar kyphosis	Scoliosis	Lumbar canal stenosis
Achondroplasia	AD	*Fibroblast growth factor receptor 3*	+++			+				+++		+++
Hypochondroplasia											++	+++
Thanatophoric dysplasia			+++	+++						+++		
Diastrophic dysplasia	AR	*Solute carrier 26A*		++	+++	+++			+++	++	++	
Spondyloepiphyseal dysplasia congenita	AD/AR	*Collagen type alpha 1 chain*			+++		+++	+++				
Kneist syndrome	AD			+		+	++	+		++	++	
Pseudoachondroplasia	AD	*Cartilage oligomeric matrix protein*			+++		+++				++	+
Metatrophic dysplasia	AD	*Transient receptor potential vanilloid type 4*		+	+							
Campomelic dysplasia	AD	*Sex determining region Y (SRY)-box 9*		++	++					++	++	
MPS I	AR	*Iduronidase*	++	++	++		++			+++		+
MPS IV		*Galactosamine-6-sulfate*	+++	+	+++		+++			++	++	
MPS VI		*Arysulfatase B*	++	+	++		++			++		

AD: Autosomal dominant; AR: Autosomal recessive; MPS: Mucopolysaccharidoses; +: Case report; ++: Common; +++: Ubiquitous.

Table 2 List of studies on surgical management of spinal disorders in achondroplasia

Ref.	Spinal disorder	Type of study	Sample size (male/female)	Mean age (years) (SD)	Total surgeries	Surgical levels decompressed	Median follow-up	Indications of primary surgery	Revision surgery indications (early)	Revision surgery indications (late)	Late revision surgery types	Complications	Outcomes
Urbanschitz *et al*[30], 2024	Thoracolumbar spinal stenosis	Retrospective	15 (8/7)	52 (10.4)	31 (primary: 12/revision: 19)	79	24 months (interquartile range: 34 months; range: 4-85	Myelopathy: 5; spinal claudication: 4; paraparesis:	3/19 (complication within 30 days: Dural tear, wound healing	16/19 (spinal stenosis: 7; hyperkyphosis: 4; adjacent segment disease:	Decompression: 5; decompression + fusion: 8; alignment	Dural tear: 11; implant failure: 2; wound disorder: 2; urosepsis: 1	Full recovery: 5; partial recovery: 11; no improvement:

							months)	2; acute foot drop: 1	disorder, adjacent segment collapse)	2; pseudoarthrosis: 2; posttraumatic deformity: 1)	correction with osteotomy: 3)		2
Hariharan *et al*[31], 2024	Spinal stenosis	Retrospective	33	18.7 (10.1)	33 (24 selected for analysis)		-	-	-			Caudal pseudarthrosis: 8; proximal junctional kyphosis: 7; new neurological symptoms: 7	
Tanaka *et al* [28], 2022	TLK	Retrospective case series	3 (2/1)	22.3	3	Posterior vertebral column resection	9.3 years	Severe TLK with neurological deficits and urinary disturbance	Surgery: Posterior vertebral column resection with cage and segmental instrumentation			Rod breakage, surgical site infection	Average Japanese Orthopedic Association score improved from 8.3/11 to 10.7/11 (mean recovery rate: 83%); 67% kyphotic angle correction
Sciubba *et al* [29], 2007	Spinal stenosis. Surgery: Decompression +/- fusion	Retrospective	44 (25/19)	12.7	60 decompressive surgeries	Thoracolumbar (65.3%), lumbar (20.4%), cervical (8%), cervico-thoracic (4%), thoracic (2%)	34 months	Neurogenic claudication (91%), pain (95.4%), cauda equina syndrome (25%), myelopathy (4.5%)	Disc herniation at L2-3 within a previous laminectomy	Progressive deformity, junctional stenosis, and recurrence of symptoms		Dural tear: 4, wound breakdown: 2, radicular pain: 3	32 patients showed improvement in symptoms
Matsumoto *et al*[32], 2006	TLK, surgery: Posterior osteotomy with segmental instrumentation	Case report	4 (3/1)	32.5	4	Thoracolumbar	35 months	Severe TLK with neurologic deficit				Dural tear and partial nerve root laceration: 2	Mean recovery rate: 75%

TLK: Thoracolumbar kyphosis.

early intervention are crucial to managing these deformities effectively. In patients with marked lumbosacral lordosis, conservative management is usually sufficient, with decompressive laminectomy rarely required.

Collagen type alpha 1 chain related disorder

Spondyloepiphyseal dysplasia: Spondyloepiphyseal dysplasia (SED) is a heritable dysplasia manifested at birth with dysgenesis of vertebral bodies, extremities, and pelvis resulting in short stature. It has two variants, SED congenita (SEDc)

and SED tarda (SEDt)[24].

SEDc is a rare autosomal dominant genetic disorder with an incidence of approximately 3/1000000[45]. The *collagen type alpha 1 chain* (*COL2A1*) gene, which controls the synthesis of type II collagen, a crucial component of cartilage and other connective tissues, is mutated in SEDc. SEDc is related to other skeletal dysplasias with type II collagen defects, such as Kniest syndrome, Stickler syndrome, and Strudwick spondylometaphyseal dysplasia[46].

Pathophysiology: SEDc is noticeable at birth, often characterized by short-trunk dwarfism and specific imaging findings. The condition leads to delayed ossification in the vertebral bodies and coxa vara, while the hands and feet usually appear normal in size. As the child grows, ossification delays in the femoral heads and irregularities in the long bones epiphyseal and metaphyseal areas continue to manifest[47].

One of the primary concerns in SEDc is atlantoaxial instability, which affects nearly half of affected children[47]. This instability, often due to odontoid hypoplasia, results in abnormal cervical spine motion in flexion or extension. Infants may show hypotonia, which generally resolves with age, but failure to reach motor milestones could indicate cervical spine issues. Atlantoaxial instability is frequently detected early, sometimes as early as one year of age.

Clinical features and management: The presence of atlanto axial subluxation with hypoplasia of the odontoid and/or lax ligaments leads to myelopathy in these cases[48]. Detecting atlantoaxial instability in young children with SEDc can be difficult due to the increased flexibility of the cervical spine and the delayed ossification of posterior elements. Although initial assessments use cervical spine radiographs, MRI in flexion-extension positions provides a more detailed view of anatomical abnormalities, SAC compression, or canal narrowing.

The approach to treating atlantoaxial instability in SEDc depends on the level of instability and the involvement of the SAC. Posterior upper cervical fusion is recommended if radiographs show movement exceeding 8 mm or if MRI reveals SAC compression or signal changes. In more severe cases, where SAC compression is significant, additional procedures like a C1 laminectomy may be required along with an occiput-to-C2 fusion. The typical surgical procedure involves fusing the occiput to C2, usually without additional wiring or instrumentation, to accommodate the developing bones of the child. A corticocancellous bone graft is utilized, followed by immobilization in a halo brace for three months to ensure the fusion is successful[49]. When deciding on the best surgical approach for atlantoaxial subluxation associated with myelopathy in SEDc, it's essential to consider whether the subluxation can be reduced and whether the space available for the SAC is narrow, especially in the presence of os odontoideum. For patients with a narrow SAC, a combination of C1 laminectomy and occipital-cervical fusion is advised[48].

For scoliosis, initial treatment with a thoracolumbosacral orthosis may be effective, but progressive cases might require posterior spinal instrumentation and fusion. Intraoperative SAC monitoring is essential for ensuring safety during these procedures.

SEDt, primarily affecting males, is caused by mutations in the *SEDt* gene. Spinal manifestations include platyspondyly, kyphoscoliosis, and early-onset osteoarthritis. Atlantoaxial instability is a significant risk, requiring careful monitoring and potential surgical intervention. Patients often experience short stature and joint pain, necessitating ongoing orthopedic and rehabilitative care.

Kniest syndrome

Kniest syndrome is a rare skeletal dysplasia resulting from mutations in the *COL2A1* gene, characterized by short stature, scoliosis, kyphosis, joint contractures, and various skeletal abnormalities[50]. Although individuals with Kniest syndrome generally have a normal life expectancy and cognitive function, they often encounter significant orthopedic challenges, particularly involving the spine and long bones. Early identification and appropriate management of these features are essential to enhance the patient's quality of life and prevent complications.

Clinical features and management: Kniest syndrome shares many clinical features with SEDc. Affected individuals typically display metaphyseal widening of the long bones, coxa vara, delayed epiphyseal ossification, and sometimes angular deformities of the lower limbs[51,52]. Due to femoral external rotation, these children often exhibit a pronounced external foot progression angle when walking. Imaging studies frequently reveal coronal and sagittal vertebral clefts in about 63% of infants with Kniest syndrome, providing a valuable diagnostic clue[51].

Odontoid hypoplasia, which can result in atlantoaxial instability, is the most prevalent spinal issue requiring treatment in Kniest syndrome. It is recommended to monitor this instability with serial flexion-extension lateral cervical spine radiographs or flexion-extension sagittal MRI scans. If surgical intervention is necessary, posterior occipitoaxial fusion may be performed, following similar criteria as those used for SEDc[53].

Scoliosis is also commonly seen in Kniest syndrome, but due to the limited growth of the trunk, it does not always require intervention. Regular thoracolumbar spine radiographs are advised to assess the progression of spinal deformities and to determine if orthotic management or surgery is needed. If surgery becomes necessary, standard spinal instrumentation, though small, is generally adequate[24].

Beyond orthopedic issues, individuals with Kniest syndrome may also experience early-onset osteoarthritis, hearing loss, and visual impairments. These additional conditions necessitate a multidisciplinary approach to care, ensuring that the wide range of health challenges associated with this syndrome are comprehensively managed[54].

TRPV4 related disorder

Metatropic dysplasia: Metatropic dysplasia, caused by *TRPV4* gene mutations, is characterized by short-limbed, short-trunk dysplasia with articular abnormalities, kyphoscoliosis, platyspondyly, and progressive spinal stenosis[55]. The pronounced spinal curvature typically presents early and progresses over time, often requiring complex surgical

interventions. Progressive kyphoscoliosis leads to a reversal of body proportions during childhood, characterized by trunk shortening and relatively long extremities. Radiographic findings include significant platyspondyly with wafer-thin vertebral bodies, widened metaphyses giving tubular bones a dumbbell-like appearance, small epiphyses, and a distinctive pelvic shape. The severe kyphoscoliosis is relentless and does not respond well to conservative bracing. Surgical treatment remains controversial due to the high risk of deformity recurrence despite aggressive correction[56]. Bauer *et al*[57] conducted a 12-year retrospective review of 20 metatropic dysplasia patients and examined severe thoracic kyphosis treatments, including observation, bracing, anterior release with growing constructs, and final fusion. Surgical patients, presenting with an average kyphosis of 86.7°, showed significant reduction, particularly with staged thoracoscopic release, halo traction, and growing rods, which achieved an average correction of 71°. Observation showed minimal progression, indicating initial non-surgical management may be viable, with effective surgical options available for progressing cases.

Cartilage oligomeric matrix protein related disorder

Pseudoachondroplasia: Pseudoachondroplasia is a type of short-limbed dwarfism inherited in an autosomal dominant manner, caused by a defect in cartilage oligomeric matrix protein (COMP) located on chromosome 19p13.1[58]. Unlike some skeletal dysplasias, this condition is not usually identified at birth due to its normal facial appearance

Pathophysiology: Pseudoachondroplasia arises from a defect in COMP, which impairs cartilage and bone development. On radiographic imaging, this condition shows characteristic changes in the epiphyses and metaphyses of long bones, and spinal images reveal flattened vertebral bodies with a central, anterior tongue-like projection. Despite these abnormalities, trunk height generally remains within normal limits.

Clinical features and management: Individuals with pseudoachondroplasia have a normal facial appearance but may develop angular deformities in the lower limbs and early-onset hip osteoarthritis.

Spinal features include increased lumbar lordosis, often due to hip flexion contractures. Proximal femoral extension osteotomies can help if the lordosis is flexible, though it tends to become more rigid with age. Thoracic kyphosis may initially be a compensatory response to lumbar lordosis but can progress into a fixed deformity requiring treatment. Initial management may involve orthotic devices, with surgery considered if anterior vertebral body wedging is observed. Unlike achondroplasia, which affects only a few vertebrae, pseudoachondroplasia kyphosis impacts multiple vertebrae with varying degrees of wedging.

Scoliosis may be present but is not distinctive for pseudoachondroplasia. When spinal fusion or instrumentation is necessary, standard-sized equipment can be used, as opposed to achondroplasia where avoiding the spinal canal is crucial.

Atlantoaxial instability, often due to general joint laxity rather than odontoid hypoplasia, is relatively common in pseudoachondroplasia. Up to 60% of patients may experience upper cervical instability, although surgery is rarely needed. Shetty *et al*[59] studied 15 Korean patients with pseudoachondroplasia for upper cervical spine instability and concluded that, although instability was increased, none of the patients developed cervical myelopathy, suggesting that regular monitoring is crucial while surgery may not be required.

Before any orthopedic procedure requiring anesthesia, it is recommended to perform flexion and extension lateral cervical radiographs to check for instability. If atlantoaxial instability is found, posterior atlantoaxial instrumentation and fusion may be required.

Mucopolysaccharidoses

Mucopolysaccharidoses (MPS), a group of lysosomal storage disorders characterized by the accumulation of glycosaminoglycans (GAGs), significantly affect skeletal development[60-62]. While Sanfilippo syndrome (MPS type III) and Scheie syndrome (MPS type V or I-S) rarely involve spinal complications, Scheie syndrome can lead to dural thickening and subsequent neurological deficits[63]. Diagnosis is usually established by appropriate serum and urine studies and by culture of either fibroblasts or leukocytes to elucidate the specific MPS syndromes. In some MPS syndromes, particularly Hurler syndrome, survival has been significantly enhanced using enzyme replacement therapy and bone marrow transplantation[64]. These modalities have advantages regarding soft tissues; however, these therapeutic modalities are not effective for bone or cartilage and MPS-related bone deformity including the spine. Because spinal disorders show the most serious deterioration among patients with MPS, spinal surgeries are required although they are challenging and associated with high anesthesia-related risks[65,66].

Pathophysiology: All spinal problems in MPS are caused by a combination of factors that include spinal canal stenosis, hypermobility/joint laxity, and skeletal deformity. Skeletal deformity arises from GAG accumulation in the prenatal chondrocytes of primary and secondary ossification centers affecting normal systemic endochondral and membranous bone growth[67,68]. It begins in the prenatal period and lasts until the growth of new bone stops. While GAG accumulation in the connective tissue of the anterior extradural space and ligamentum flavum results in spinal canal stenosis, it can also cause inflammation and degradation of surrounding tissue in the spinal ligament and capsule of facet joints, leading to hypermobility and joint laxity[69,70]. Atlantoaxial instability is frequently observed in MPS IV followed by MPS VI and MPS I. TLK is a well-known hallmark of MPS I but is also common in MPS II, IV, and VI. Cervical stenosis is broadly recognized in all MPS types except for MPS III[69,71,72].

Clinical features and surgical management

Atlantoaxial instability: Atlantoaxial instability is common in MPS IV and VI, associated with dens hypoplasia,

ligamentous laxity, and GAG accumulation. This can lead to severe complications like SAC damage, sudden death, or quadriparesis. Neurological symptoms vary and can include numbness, clumsiness, and gait instability, often complicating diagnosis due to communication issues or joint contractures in patients.

Diagnosis typically involves flexion/extension radiographs and MRI, though computed tomography (CT) scans offer a better assessment of odontoid hypoplasia. Surgical intervention, such as fixation/decompression, is crucial before irreversible damage occurs, but the timing remains controversial. It should be reserved for demonstrable cervical instability rather than performed prophylactically. Challenges in surgery include the difficulty of instrument fixation in small vertebrae and the potential need for revision surgery due to adjacent instability[73-75]. In pediatric cervical spine surgery, rigid fixation of the C1-C2 joint promotes higher fusion[76]. Occipital plates, multiaxial lateral mass, intralaminar, trans articular, and pedicle screws allow various construct options. Laminoplasty or laminectomy is recommended depending on the stability and maturity of the cervical vertebrae. Long-term follow-up is necessary due to the risk of stenosis recurrence and complications[69].

Cervical stenosis: Cervical stenosis is widely recognized in MPS I, II, VI, and VII. There are two pathophysiological factors in spinal stenosis in MPS: (1) Developmental factors; and (2) Acquired factors. Developmental spinal canal stenosis is classified into two types: (1) Hereditary-idiopathic stenosis; and (2) Skeletal growth disorder-related stenosis-like MPS[69]. Acquired factors are related to GAG accumulation in the connective tissues surrounding the epidural space, especially in the subligamentous membrane between the dura and the ligamentum flavum, a hypertrophied ligamentum flavum, degenerated facet joints, and intervertebral discs[77]. Therefore, for complete decompression, these deposits must be removed. Symptoms depend upon the level [craniovertebral junction (CVJ) is the most common level] and the severity of stenosis. C1 hypoplasia with atlantoaxial instability is commonly seen in MPS IV and VI. In most cases, the initial symptom of cord compression is numbness in both hands. Neck extension test, Phalen's test and Tinel's sign is necessary for diagnosis, as carpal tunnel syndrome is also common in MPS[72]. MRI is required to establish the diagnosis. Hypertrophic changes in circumferential epidural space caused by GAG accumulation and thickened ligamentum flavum compressing on underlying cord (loss of CSF rim) with intramedullary T2 hyperintensity is suggestive of irreversible cord damage[78]. Patients with cervical stenosis should undergo decompressive surgery before irreversible cord damage occurs. Posterior decompression surgery without instrumented fixation is appropriate for patients without obvious cervical instability. Laminoplasty with hydroxyapatite spacers is preferred over total laminectomy to avoid complications, instability, and post-laminectomy fibrosis. C1 laminectomy is often recommended with C2-C7 laminoplasty, and suboccipital decompression should be considered for occipital-cervical stenosis. In young patients with immature cervical laminae, total laminectomy is the only option, requiring long-term monitoring for recurrence due to instability or fibrosis [69,79]. A study by Kawaguchi *et al*[80] found that 49.2% of patients who underwent laminoplasty more than 20 years ago experienced worsened outcomes, often requiring additional surgeries.

TLK: TLK is a common feature in MPS I, affecting up to 90% of patients despite hematopoietic stem cell transplantation. It also occurs in MPS II, IV, and VI. Scoliosis may coexist with kyphosis or appear alone in MPS I, II, and III, but surgical intervention for scoliosis is rare unless significant kyphosis is present[60]. The characteristic vertebral shape in MPS, called platyspondyly, results from incomplete endochondral ossification, with terms like coined or beaked vertebrae describing the deformity[81]. TLK leads to sagittal imbalance, requiring compensatory postures to maintain standing balance. There is no consensus on the ideal timing or method of surgery or the effectiveness of bracing for TLK in MPS. Kyphosis exceeding a 40-degree Cobb angle tends to progress, particularly in MPS I, and the impact of enzyme replacement therapy or bone marrow transplantation on spinal deformity remains unclear[82]. Bracing has shown some success in preventing kyphosis progression in MPS I, but further research is needed. Progressive kyphosis with neurological deficits is a clear indication for surgery. Postoperative complications can include death, neurological deficits, pseudarthrosis, infection, junctional deformity, and anesthesia-related issues, with thoracic SAC ischemia possibly leading to paraplegia[60,83].

Lumbar canal stenosis: The incidence of lumbar canal stenosis (LCS) is increasing in MPS cases due to increased life expectancy. Hypertrophy of the ligamentum flavum, degenerative changes in facet joints, and bulging intervertebral discs are key factors in degenerative LCS, with bone deformities contributing to LCS in MPS patients. Symptoms of LCS include intermittent claudication, low-back pain, and bowel/bladder dysfunction. Surgical indications for LCS in MPS patients are similar to those in non-MPS patients, with posterior decompression sufficient if there is no significant spinal instability. Instrumented fusion is indicated only if instability affects symptoms. There are no long-term follow-up data on LCS surgery in MPS patients[69].

Hurler Syndrome (MPS type I)

Infants with Hurler syndrome appear normal at birth. However, short stature and delayed developmental milestones become apparent early. TLK and atlantoaxial instability with thickening of alar ligaments are common. Kyphosis becomes apparent clinically only after the child starts sitting. In the past, surgical management was not indicated as life expectancy was not beyond early childhood. In the present, however, there has been significant improvement in quality of life and survival due to the utilization of enzyme replacement therapy and bone marrow transplantation. In one group of 10 patients followed for a mean of 8.7 years after bone marrow transplantation, all showed a decrease, however, in the amount of odontoid dysplasia[84]. Laboratory studies show excessive dermatan sulfate and heparin sulfate secretion. Yasin *et al*[85] treated five MPS-I patients with progressive TLK using anterior vascularized rib grafts, correcting the kyphosis angle from 53° to 44°. However, this method has drawbacks such as graft dislodgement and hyperlordosis. Dalvie *et al*[86] reported on anterior instrumented fusion in seven MPS patients, noting technical challenges and neurological risks. For kyphosis over 60°-70°, combined anterior and posterior fusion is recommended[86].

Hunter syndrome (MPS type II)

Hunter syndrome, an X-linked recessive lysosomal storage disease affecting males, is caused by a defect in iduronate-2-sulfatase, leading to the buildup of GAGs and resulting in neurological issues. Although children with Hunter syndrome appear normal at birth and grow typically for the first two years, abnormalities usually become apparent afterward. While life expectancy can extend into adulthood, cardiopulmonary complications may lead to death in the second decade of life. The syndrome is characterized by non-specific vertebral changes, with some cases of marked lumbar kyphosis requiring surgery. MRI evaluation of the upper cervical spine is crucial due to potential SAC compression from mucopolysaccharide deposition behind the odontoid.

Morquio syndrome (MPS type IV)

Morquio syndrome, a type of MPS, typically presents normal at birth, but by the first year, developmental delays and physical changes like TLK, short stature, genu valgum, pectus carinatum, and corneal clouding become noticeable. The syndrome is marked by anteroinferior vertebral beaking, hip subluxation, and decreased exercise tolerance due to hip instability, knee valgus, or potential SAC compression. Odontoid hypoplasia often leads to atlantoaxial instability, requiring cervical spine evaluation before orthopedic surgery. If instability is detected, posterior cervical fusion is recommended. TLK, present at birth, usually remains stable, with surgery considered if progression occurs, often combining pedicle screw instrumentation with laminectomy or anterior spinal instrumentation for safety.

Maroteaux-lamy syndrome (MPS type VI)

MPS Type VI is a rare autosomal recessive lysosomal storage disease caused by impaired catabolism of dermatan sulfate. Deficiency of the enzyme arylsulfatase B leads to progressive accumulation of partially degraded dermatan sulfate within a variety of tissues with consequent clinical manifestations such as hearing impairment, organomegaly, bone dysplasia, cardiorespiratory and neurological problems. Many of the physical features resemble Hurler syndrome, but intelligence is normal. Neurologic manifestations are often due to bone abnormalities resulting in SAC or nerve root compression, carpal tunnel syndrome, optic nerve compression, jugular foramen stenosis, and communicating hydrocephalus Bulut *et al*[87] retrospectively evaluated spinal MRI scans and clinical findings in 14 patients of MPS VI. CVJ anomalies (low clivus-canal angle; odontoid dysplasia, FMS, and thickened retrodental tissues), TLK, platyspondyly and anteroinferior beaking of cervical vertebrae, posterior focal end plate depression in thoracic vertebrae, posterior scalloping and anterior beaking of lumbar vertebrae were the most predominant findings in their study. SAC compression is more commonly found in MPS VI and IV compared to MPS I. CVJ is the most common site of SCC, but can occur at any level. Bony stenosis due to small and thickened posterior elements, thickened retrodental tissue, and odontoid dysplasia are commonly recognized causes of cervical cord compression in MPS VI. Thickening of the retrodental tissue is secondary to hypertrophy of the cruciate and posterior longitudinal ligaments as well as dural accumulation of GAGs, similar to that seen in more common type MPS 1.

Osteogenesis Imperfecta (OI)

OI, known as brittle bone disease, results from mutations in collagen genes (*COL1A1* or *COL1A2*), leading to fragile bones and multiple fractures. Progressive scoliosis is common in severe forms of OI, significantly impacting pulmonary function and quality of life. Recurrent vertebral compression fractures lead to kyphosis and chronic pain. Basilar invagination, the upward displacement of the upper cervical spine into the skull, causes neurological deficits and requires surgical intervention. Management of OI also includes addressing frequent long bone fractures, dentinogenesis imperfecta, and hearing loss, necessitating a comprehensive and multidisciplinary approach.

Cervical myelopathy due to stenosis at the foramen magnum and upper cervical spine can be treated by laminectomy. Early detection and treatment of cord compression are crucial to preclude irreversible neurologic impairment. Lampe *et al* [74] developed a scoring system using findings of neurological examination, somatosensory-evoked potentials of median nerve and MRI of craniocervical junction to establish objective criteria for decision of cervical decompression surgery in MPS VI. The sum of the scores of each procedure, so-called craniocervical cord compression score, was revealed to be a reliable tool for determining need and correct timing of surgery. Progressive TLK can be treated by posterior instrumentation and fusion. Intraoperative neurophysiological monitoring during posterior instrumentation is recommended to avoid iatrogenic neurological injury as there is a narrow spinal canal.

Multiple epiphyseal dysplasia (MED), caused by mutations in genes such as COMP, COL9A1, and matrilin, especially matrilin-3, affects epiphyseal development, leading to joint and spinal abnormalities[88]. Mild scoliosis and TLK are common, causing discomfort and potential respiratory issues. Early-onset osteoarthritis due to abnormal epiphyseal growth further complicates the clinical picture. Patients with MED may also have short stature, joint pain, and early degenerative changes, necessitating a multidisciplinary approach for optimal management.

Chondroectodermal dysplasia [Ellis-van Creveld (EVC) syndrome] involves skeletal abnormalities, short stature, and polydactyly, caused by mutations in the *EVC* or *EVC2* genes[89]. Spinal manifestations include lumbar lordosis and mild scoliosis, which can lead to mobility issues and discomfort. Additionally, patients often present with congenital heart defects, dental anomalies, and nail dysplasia, requiring comprehensive care from multiple specialties[90].

Spondyloepimetaphyseal dysplasia, Strudwick type encompasses a group of disorders affecting the spine and metaphyses of long bones. Spinal manifestations include kyphoscoliosis, platyspondyly, and spinal stenosis. These conditions lead to significant morbidity due to progressive spinal deformities and neurological impairments. Joint abnormalities and early-onset osteoarthritis further complicate the clinical picture, requiring a comprehensive and multidisciplinary management approach[91-93].

Table 3 Summary of surgical management of spinal disorders in various skeletal dysplasias

Skeletal dysplasia (incidence)	Common spinal disorders	Nonsurgical management	Surgical management
Achondroplasia (1:20000-1:30000)	Foramen magnum stenosis neurological complications	Regular monitoring with magnetic resonance imaging and X-rays. Physical therapy for posture and strength. Pain management. Ergonomic modifications	Decompression surgery if severe compression or neurological symptoms occur
Hypochondroplasia (1:15000-1:40000)	Spinal stenosis: Degenerative disc disease	Physical therapy. Pain management. Ergonomic modifications. Regular spinal assessments	Surgical intervention for severe stenosis or radiculopathy. Decompression surgery
Spondyloepiphyseal dysplasia congenita (1:100000)	AAI, OH, scoliosis	Physical therapy. Bracing for scoliosis. Regular monitoring. Pain management. Adaptive mobility devices	Decompression (C1 laminectomy) and OC fusion. Deformity correction
Kniest dysplasia (1:1000000)	AAI, OH, scoliosis	Physical therapy. Bracing for scoliosis. Regular monitoring. Pain management. Adaptive mobility devices	Decompression (C1 laminectomy) and OC fusion. Deformity correction
Diastrophic dysplasia (1:500000)	Cervical kyphosis, kyphoscoliosis	Early orthotic management. Regular monitoring for curve progression. Physical therapy. Pain management	Anterior/posterior correction for severe curves or progressive deformities. Spinal fusion if necessary
Mucopolysaccharidoses (all forms: 1:25000, I: 1:100000, IV: 1:200000-1:300000)	Craniovertebral junction stenosis, Thoracolumbar kyphosis, scoliosis	Regular monitoring and physical therapy. Management of symptoms and pain. Occupational therapy. Supportive care	Deformity correction. Decompression if necessary
Osteogenesis imperfecta (all forms: 1:10000-1:20000)	Spinal deformities (kyphosis, scoliosis)	Regular spinal evaluations. Bracing and physical therapy. Bisphosphonates for bone strength. Pain management	Surgery for severe curves or spinal instability. Spinal fusion in progressive cases

AAI: Atlantoaxial instability; OC: Occipitocervical; OH: Odontoid hypoplasia.

Effective management of spinal manifestations in skeletal dysplasia involves a multidisciplinary approach, including orthopaedic surgeons, neurologists, geneticists, and rehabilitation specialists. Early diagnosis and monitoring through regular imaging (X-rays, MRI, CT scans) and clinical evaluations are crucial to track the progression of spinal deformities and detect complications early. Surgical interventions, such as decompression, spinal fusion, and corrective osteotomies, are indicated for severe deformities or neurological deficits. Non-surgical management, including bracing and physical therapy, helps control the progression of deformities and improve functional outcomes. Genetic counseling is essential for affected families to understand the hereditary nature of these conditions and the risk of recurrence in future pregnancies. Comprehensive care involves coordination among various specialties to address the complex needs of patients, including respiratory care, pain management, and rehabilitation (Table 3).

CONCLUSION

Spinal manifestations in skeletal dysplasia demand a multidisciplinary approach encompassing early diagnosis, close monitoring, and individualized treatment strategies. While conservative measures provide symptom relief in some cases, surgical intervention is often warranted for progressive deformities and neurological compromise. Future research should focus on refining surgical techniques, improving long-term outcomes, and exploring novel therapeutic approaches, including gene therapy and targeted molecular treatments. By addressing these challenges, clinicians can enhance the quality of life and functional outcomes for patients with skeletal dysplasia.

FOOTNOTES

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MINIREVIEWS

Present status and future directions: Soft tissue management in prosthodontics

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Abstract

During restorative dental procedures, complete control over the operative site is critical for patient comfort, safety, and the operator's access and visibility. The success of a fixed prosthesis depends on accurate impression making of the prepared finish lines on the abutment teeth. To optimise long-term outcomes for the fixed restoration, gingival retraction techniques should be used to decrease the marginal discrepancy among the restoration and the prepared abutment. Accurate marginal positioning of the restoration along the prepared finish line of the abutment is essential for therapeutic, preventive, and aesthetic purposes.

Key Words: Soft tissue; Prosthodontics; Fixed prosthesis; Dentistry; Implants

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Core Tip: The primary goal of soft tissue management in prosthodontics is to improve visibility and accessibility, particularly when working with complex or obscure microanatomy over an extended period. Effective manipulation of soft tissues facilitates highly accurate impressions, superior prosthesis adaptation, and enhanced long-term clinical outcomes. However, soft tissue management remains underutilised in general practice despite its significance. This is largely due to behavioural factors such as clinician hesitation, lack of specialised training, patient discomfort, and time constraints. Overcoming these challenges requires education, advanced techniques, and patient-centred approaches to improve clinical outcomes.

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INTRODUCTION

The difficulties that arise from the labial, buccal mucosa and tongue, along with the challenges of accessing and operating instruments, and the positioning of treated teeth concerning the gingival tissues, which can bleed if not properly handled, render the oral cavity a complex area for treatment in prosthetic dentistry[1]. The dental dam usually serves a valuable purpose in operative dentistry and single-tooth restorations by providing field control and facilitating access to tooth preparation and restoration; however, its use is not universal in restorative dentistry. At times, caries or non-carious cervical lesions may be located at or beneath the free margins of the gingiva. In fixed prosthodontics, positioning crown or inlay/onlay margins at or below this margin can complicate preparation, impression, and cementation access. Additional techniques are often required to displace gingival tissues and manage gingival haemorrhages and sulcular fluids effectively[2]. One of the most discerning aspects of crown and bridge procedures is handling the gingival tissues during the impression process[3].

The process of impression making for fixed partial dentures is highly technique-sensitive, as it necessitates an accurate reproduction of the finish lines. Consequently, before obtaining an impression, it is essential to retract the gingival sulcus. Whether using a traditional impression material or a digital technique, the rationale for tissue management plays a crucial role in impression making. This ensures that the impression precisely replicates all margins of the tooth preparation, resulting in a superior marginal fit for a laboratory-made restoration. Once the final restoration aligns with the tooth preparation and undergoes cementation, it aids in preventing recurrent dental decay, tooth sensitivity, and gingival irritation[4]. The mechanical, surgical, or chemical widening of the gingival sulcus pushes gingival tissues surrounding the preparation edges, allowing enough low-viscosity impression material to fill the larger space and preserve the detail of the edges without compromising periodontal health[5].

The three primary goals to achieve an accurate impression are isolation, retraction, and accessibility. The operative site is isolated to ensure a dry and clean operating area, to ensure easy access and clear visibility, enhance properties of dental materials, protect both the patient and the operator, and promote operational efficiency[6]. The critical sulcular width seems to be around 0.2 mm. A width of less than 0.2 mm leads to impressions that are more likely to have voids in the marginal area, an increase in tearing of the impression material, and a decrease in marginal accuracy. Inadequate tissue management can result in enduring damage to soft tissue. The impression must be free of air bubbles, thin spots, and any other imperfections that could lead to inaccuracies[7].

Several studies have found specific factors that influence the outcome of an impression: Tissue health, fluid control, and exposure at the finish line. The purpose of gingival retraction is to gently make it easier for the impression material to reach beyond the edge of the abutment and to make room for enough thickness of impression material in the gingival sulcus area so that it can better withstand the forces used to remove impressions[8-10]. Mechanical, chemical, surgical, and various combinations of these methods are categories into which gingival displacement techniques fall. Most of the operator use a mix of mechanical and chemical methods to move the gingiva back into place. This is done by using gingival retraction cords along with certain hemostatic agents. Practitioners utilize soft tissue lasers and surgical methods, such as rotary gingival curettage and electrosurgery, as supplementary procedures alongside mechanical and chemical techniques[11-13].

CLASSIFICATION OF GINGIVAL TISSUE RETRACTION

Figure 1A shows surgical retraction (gingivectomy and gingivoplasty, periodontal flap procedures, electrosurgery, and rotary gingival curettage), according to Barkmeier and Williams[14]; non-surgical retraction (rubber dam and clamps, retraction cord-impregnated/non-impregnated, retraction rings, and copper bands)[15]. Figure 1B shows the classification of gingival tissue retraction: Conventional and radical. According to Benson *et al*[16], Figure 1C shows the classification of gingival tissue retraction: (1) Mechanical method: Gingival protector, rubber dam, copper band (or) tube, anatomic retraction caps, retraction cords, and special cords; (2) Chemi-mechanical method: Vasoconstrictors, biological fluid coagulants, and surface layer tissue coagulants; (3) Rotary gingival curettage; and (4) Electrosurgical methods. The goal of gingival retraction is to gently make it easier for the impression material to reach beyond the edge of the abutment

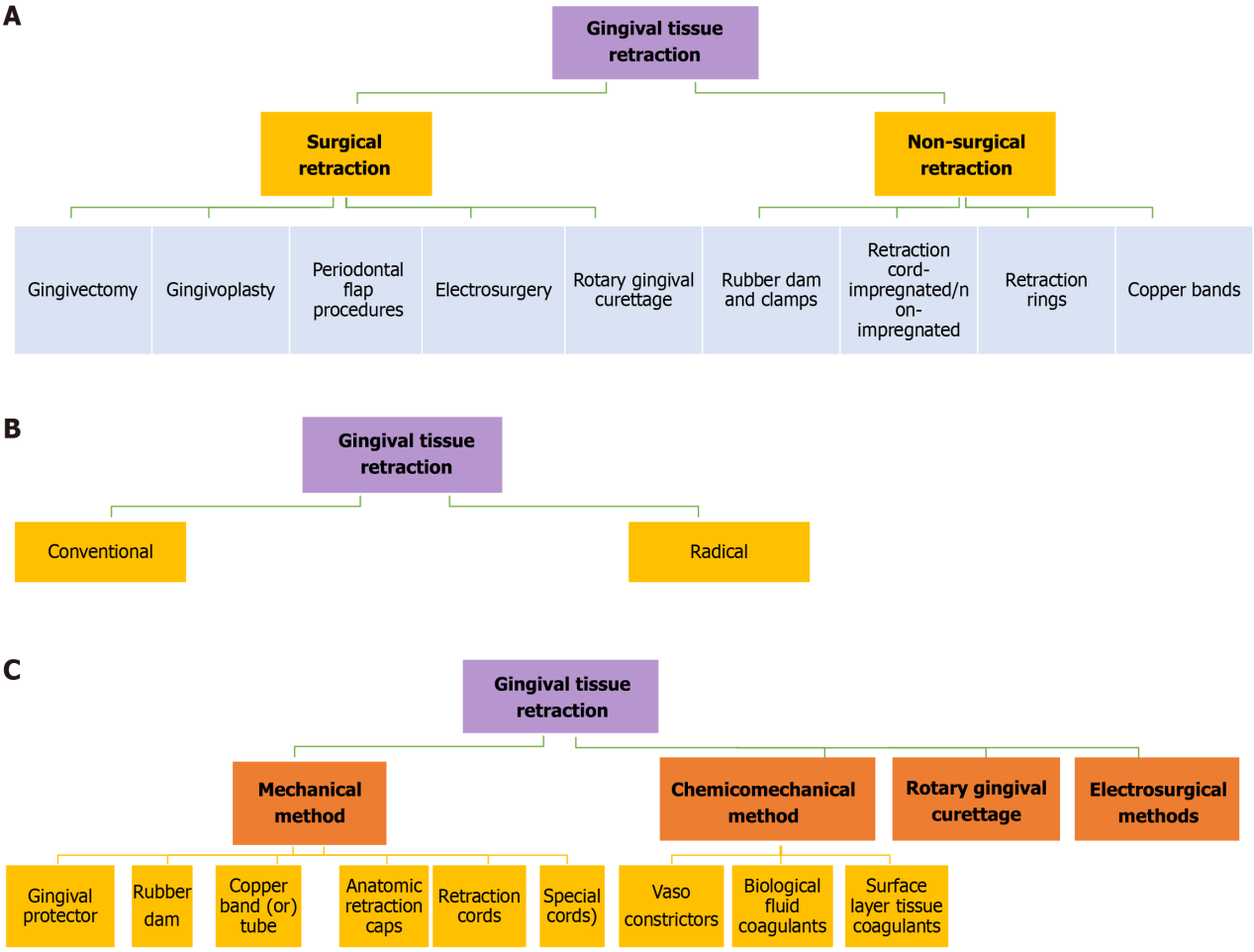


Figure 1 Classification of gingival tissue retraction. A: The classification of surgical and non-surgical gingival tissue retraction; B: The classification of conventional and radical gingival tissue retraction; C: The classification of gingival tissue retraction methods.

and to create space for enough thickness of impression material in the gingival sulcus area so that it can resist pulling forces better when impressions are taken out. The well-structured, fiber-rich periodontal complex around natural teeth supports these gingival tissues during retraction, which keeps these tissues from falling apart when the retraction agents are taken out before the impression is made[3,5].

The importance of finish line exposure in prosthodontics: (1) It is a line of demarcation; (2) The peripheral extension of a tooth preparation; (3) The planned junction of two materials; and (4) The terminal portion of the prepared tooth. Gingival tissue must be healthy and free of inflammation before fabricating cast restorations, and this impression must precisely replicate the final result. For optimal marginal fit and to avoid recurring cavities and gingival inflammation, temporarily expose the finish line to reproduce the entire preparation. Obtaining a complete impression is difficult when the preparation's finish line is at or below the crest of the free gingiva. To ensure complete reproduction of the preparation, temporarily expose the preparation's finish line. It is important to keep fluids under control in the sulcus, especially when using hydrophobic impression materials[7,8]. Advantages: (1) Provides maximal exposure to the operating site; (2) Better marginal fit; (3) Prevents tissue from trauma; and (4) Helps in better preparation and impression.

Gum protector

This tiny device has a crescent-shaped tip that can be positioned and adjusted to the contours of the gum tissue to protect the gums during procedures near the gum margins[16]. They are helpful for subgingival cavity removal, cavity preparation, finishing veneer margins, and verifying the proper seating of crowns with subgingival margins in Figure 2A [17].

Copper band

This carries the impression material and displays the gingiva to expose the finish line. The band uses either impression compounds or elastomeric materials. The tube is carefully positioned, containing the modelling compound along the tooth preparation path to make an impression[17]. The copper bar is shaped into a tube corresponding to the size of the prepared tooth. One tube end is trimmed to match the profile of the gingival finish line, followed by the positioning and contouring of the tube over the prepared tooth before filling it with the modelling compound as shown in Figure 2B[18]. They are beneficial in situations in which several teeth have been prepared. The disadvantages include copper bands carrying incisional injuries to the gingiva and gingival recession.

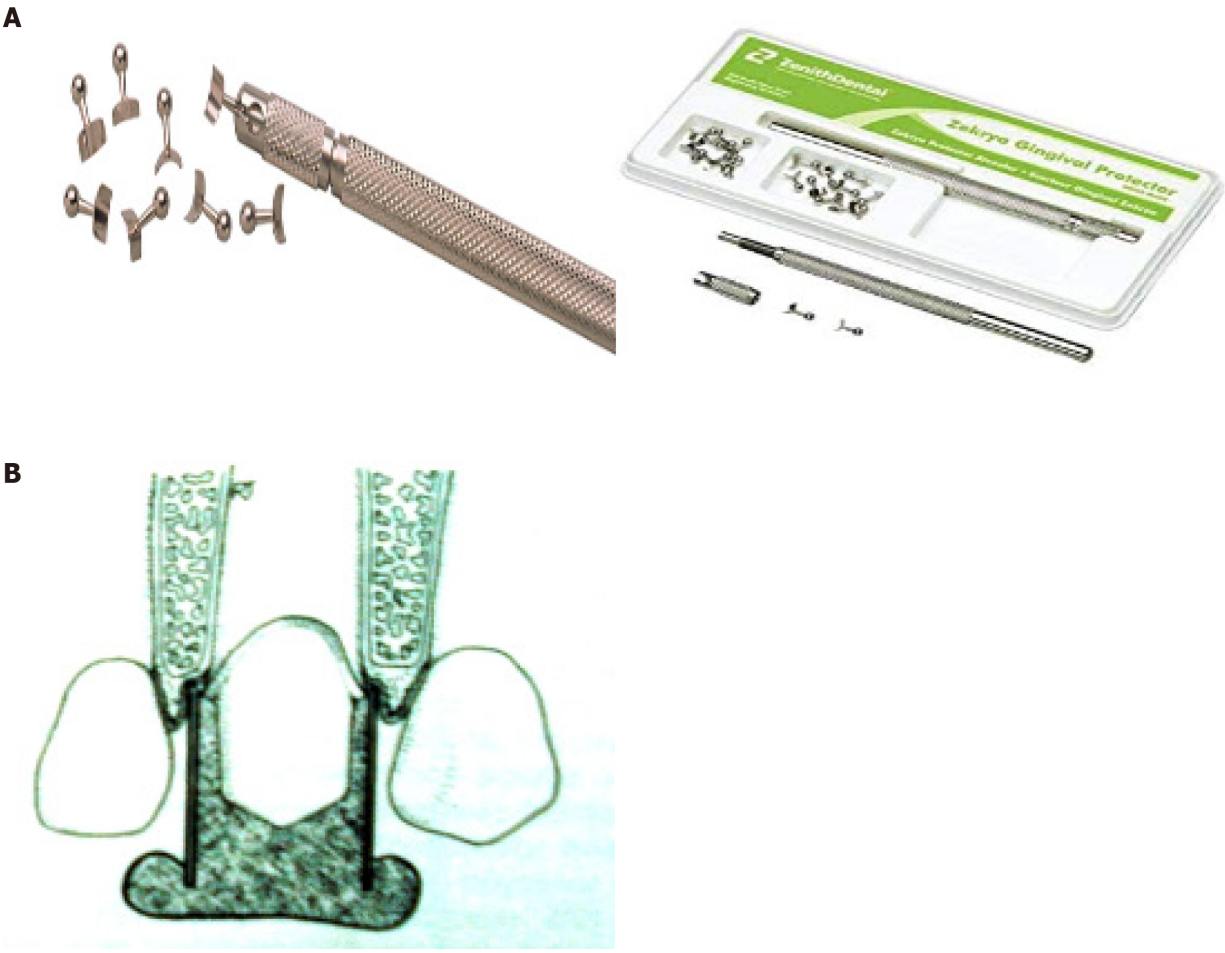


Figure 2 Gum protector and copper band. A: The gingival protector; B: The copper band.

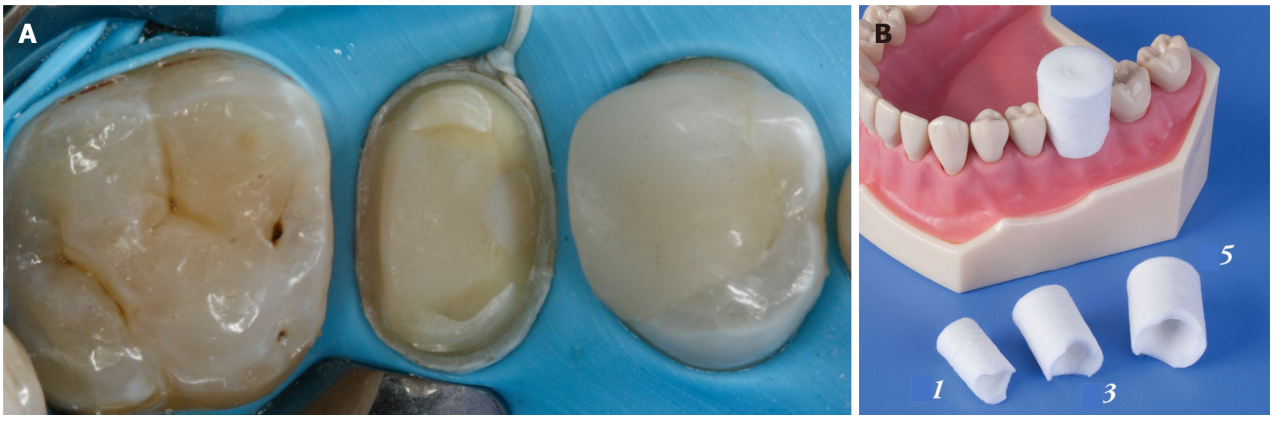


Figure 3 Rubber dam and anatomic retraction cap. A: The role of the rubber dam in fixed bridge isolation; B: The anatomic retraction cap.

Rubber dam

In 1864, New York City dentist S.C. Barnum introduced the rubber dam to dentistry. The rubber dam keeps teeth dry and enhances the quality of restorative dentistry. A rubber dam can also expose the necessary finish line. It is typically used when a few teeth in one quadrant are being restored and when preparations do not need to extend far subgingival. The advantages are a dry, clean operating field, maximum access and visibility of tooth and the margins, improved properties of dental materials, protection of the patient and operator, and operating efficiency. Time consumption and patient objection are the most frequently quoted disadvantages of the rubber dam[19]. The role of the rubber dam in fixed bridge isolation is shown in Figure 3A. Isolating one or more abutment teeth of a fixed bridge is sometimes necessary. The restoration of an adjacent proximal surface and the cervical restoration of an abutment tooth indicate the need for fixed bridge isolation[19,20].

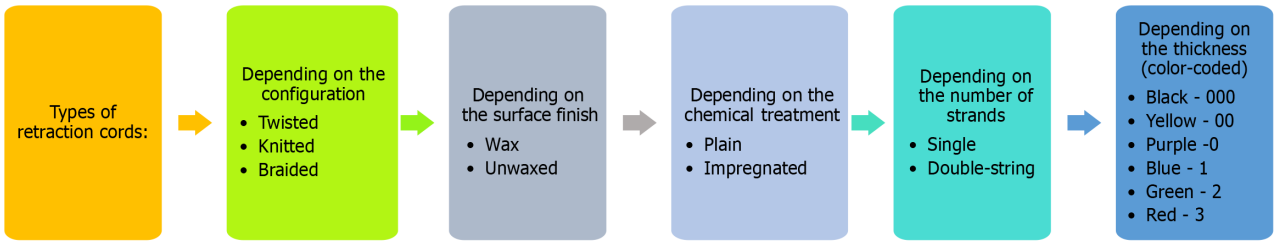


Figure 4 The types of retraction cord.

The techniques suggested for this procedure are as follows: Punch the rubber dam as usual, but create one large hole for each unit in the bridge. Once the dam is complete, the fixed bridge isolates itself. A curved suture needle with dental floss is threaded from the front through the anterior abutment hole, under the anterior connector, and back through the same hole on the backside[19]. The needle is reversed and passed from the lingual side through the hole of the second bridge unit, under the anterior connector, and through the hole of the second bridge unit on the facial side. A square knot is tied with the floss ends, pulling the dam material tightly around the connector and into the gingival embrasure. Cut the free ends of the floss closely to avoid interfering with access and visibility or getting entangled in a rotating instrument. This method isolates each terminal abutment of the bridge.

If the floss knot on the front interferes with the cervical restoration of an abutment tooth, the operator can tie the septum from the back. To remove the rubber dam from a fixed bridge, cut the interseptal rubber over these connectors with scissors and take out the floss ties[20]. After dam removal, the operator must ensure that no dam segments are missing and should gently manipulate the adjacent gingival tissue. The retainer's jaws often hinder the correct positioning and wedging of the matrix band on the posterior anchor tooth. The successful application of the matrix can be achieved by replacing the retainer with the matrix[20,21]. The operator's index finger pushes the rubber dam down on the facial jaw, while the assistant does the same on the lingual side. When the band is placed, the dam inverts around it due to the released tension. The matrix lacks jaws and a bow, which can cause the dam to slip occlusally and over the matrix if dryness is not maintained. The operator gains access and visibility for alloy insertion by using a mirror to reflect the dam distally and occlusally. Care must be taken not to stretch the dam excessively, as this can cause it to detach from the matrix, leading to leakage around the tooth or slippage over the matrix. After condensation, carve the occlusal portion before removing the matrix. The operator can complete the procedure by either: (1) Removing the matrix, replacing the retainer, and finishing the carving; and (2) Removing the matrix and rubber dam and then completing the carving. Replace the retainer before finishing the carving to ensure isolation during this procedure[19-21]. The anatomic retraction cap is shown in Figure 3B. The traction cap works similarly to a copper band, but its shape is pre-designed to simply be placed between the teeth. Once positioned, the patient bites down on the cap. Physical pressure stops the bleeding and opens the groove for the final impression[22].

Retraction cords

Gingival tissue displacement is most commonly achieved using retraction cords, which are available in various forms, including knitted, twisted, and braided. These cords can be impregnated with medicaments or hemostatic agents or left non-impregnated. Since there is no standardised sizing system, clinicians can choose the configuration that best suits their needs. Retraction cords are colour-coded and available in different diameters, typically numbered from 000 to 3, to accommodate various clinical situations and sulcus depths. They can be dispensed in pre-cut lengths corresponding to tooth diameters or from a container or clicker.

Ideal properties of retraction cord

An ideal retraction cord should: (1) Be biocompatible and non-toxic; (2) Absorb blood, crevicular fluids, and medicaments effectively; (3) Be easy to insert and remove; (4) Have a color that contrasts with surrounding tissue; and (5) Avoid causing damage to supporting tissues[23]. Figure 4 shows the types of retraction cords. The indications for different thickness cords are shown in Table 1.

Characteristics of different retraction cords

Braided cords have a tightly woven structure, making them easy to place without fraying, as shown in Figure 5A. They offer excellent absorption when used with medications. However, applying pressure to one section may cause another segment to dislodge from the sulcus. Knitted cords are designed with interlocking loops, which provide flexibility and passive adaptation during placement (Figure 5B). This feature prevents movement when another section is inserted into the sulcus. Knitted cords tend to compress upon insertion, so a slightly thicker size is recommended for optimal stability and tissue displacement. To prevent unravelling, a smooth, non-serrated instrument should be used during placement [24]. Twisted cords have a higher tendency to fray and untwist during placement, making them less commonly used compared to braided and knitted cords in Figure 5C. The Stay-Put retraction cord features a fine central wire, available in both plain and pre-impregnated versions (Figure 5D). Its key advantage is that it maintains its shape after placement. The pliability of the cord allows for easy insertion and pre-shaping. The pre-impregnated version contains aluminium chloride, which minimises cardiovascular risks. Available in four sizes (0-3), it can be used with compression caps in both standard and anatomical shapes. The anatomical compression cap has a semicircular design on the facial and lingual

Table 1 Indications for different thickness cords

Cord	Indications
000	Anterior teeth
	Double packing
	Substitute for black silk suture as lower cord in the "two-cord"
	technique
00	Preparing and cementing veneers
	Restorative procedures dealing with thin, friable tissues
0	Lower anteriors
	When luting near gingival and subgingival veneers
	Class III, IV and V restorations
	Second cord for "two-cord" technique
1	Tissue control and/or displacement when soaked in coagulative hemostatic solution prior to and/or after crown preparations
	Protective "pre-preparation" cord on anteriors
2	Upper cord for "two-cord" technique
	Tissue control and/or displacement when soaked in coagulative
	Hemostatic solution prior to and/or after crown preparations
	Protective "pre-preparation" cord on anteriors
3	Areas that have fairly thick gingival tissues where a significant amount of force is required
	Upper cord for those desiring the "two-cord" technique

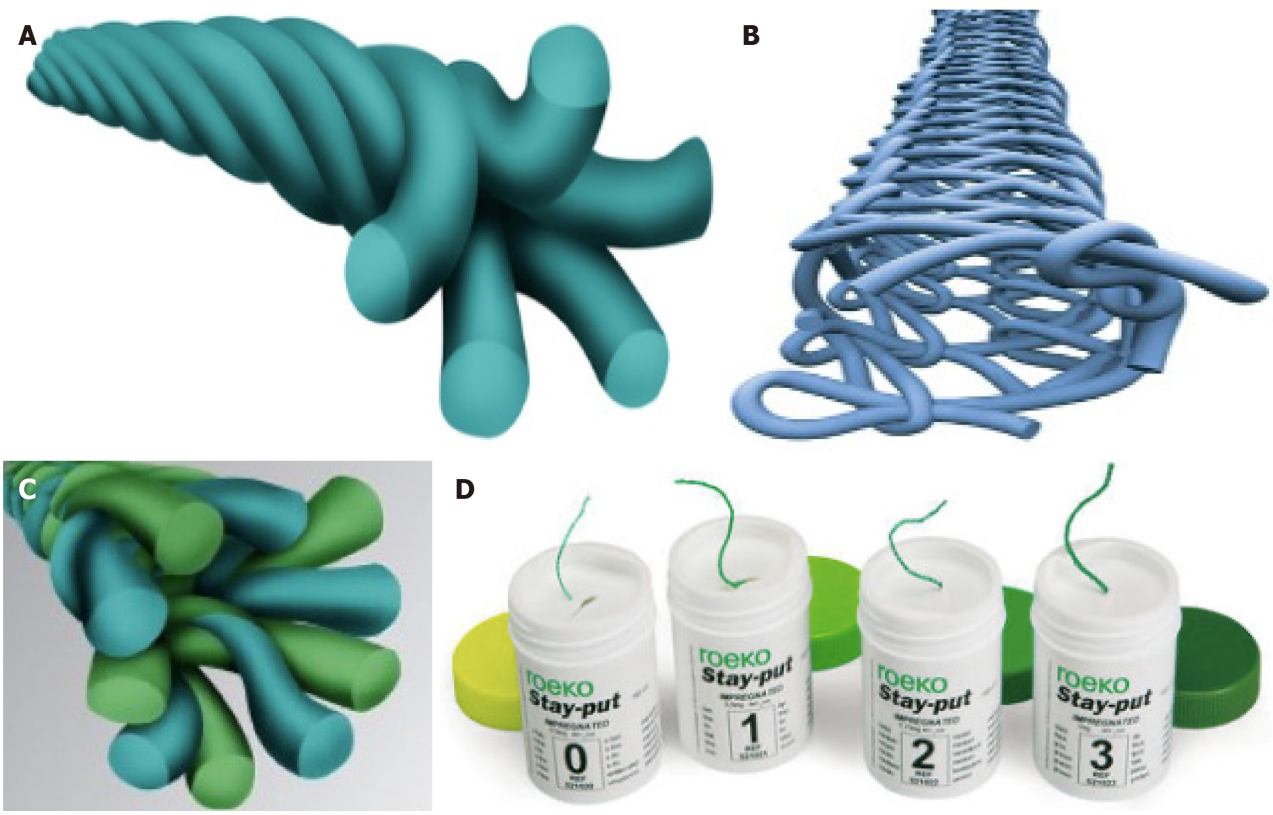


Figure 5 Characteristics of different retraction cords. A: The braided cord; B: The knitted cord; C: The twisted cord; D: The stay-put retraction cord.

Table 2 The advantages and disadvantages of different chemical agents

Chemicals	Advantages	Disadvantages
Epinephrine	Good tissue displacement	Systemic reactions
	Minimal tissue loss	Epinephrine syndrome
	Good hemostasis	Risk of inflammation of the gingival cuff
		Rebound hyperemia
		Risk of tissue necrosis
Alum	Minimal tissue loss	Less hemostasis and tissue displacement
	Extended working time	Offensive taste
		Risk of necrosis if in high concentration
Aluminum chloride	Minimal tissue loss	Local tissue destruction
	Good hemostasis	Less vasoconstriction than epinephrine
	No systemic effects	Risk of sulcus contamination
	Least irritating of all chemicals	Modifies surface detail reproduction
	Hemostasis	Inhibits set of polyvinyl siloxane and polyether impressions
	Little sulcus collapse after cord removal	
Ferric sulfate	Compatible with aluminum chloride	Non compatible with epinephrine
		Tissue discoloration
	Good displacement	Acidic taste
		Risk of sulcus contamination Inhibits set of polyvinyl siloxane and polyether impressions
Tannic acid	Good tissue response	Less displacement
		Minimal hemostasis

sides that can be placed over neighbouring teeth to enhance traction. After inserting the cord, the compression cap is placed over the tooth, and the patient is then instructed to bite down. This technique further promotes gingival sulcus traction[25].

Chemo-mechanical methods

This method uses a traction cord and chemicals or medications. There is a wide variety of materials used with gum retractors. These chemicals can be pre-impregnated into the gingival retractor or soaked into a traditional gingival retractor before insertion[26]. The primary effect of all these chemicals is to stop bleeding and reduce crevicular fluid leakage while physically displacing the gingival tissue[27]. They can be vasoconstrictors that force blood vessels to constrict, astringents that shrink gum tissue, or substances that stop bleeding by hemostasis and clotting. Some of the therapeutic agents are gel or liquid formulations that can be injected directly into the gingival sulcus to stop bleeding and gingival fluid[28-30]. Chemicals used for this purpose can be classified by their actions (Figure 6). The advantages and disadvantages of these chemical agents are shown in Table 2[30].

Cord packing instrument

The retractable cord filler is designed to insert the retractable cord into the gingival sulcus (Figure 7A)[31]. Nevertheless, many medical professionals use a variety of tools for this purpose. It is important that whichever tool is used, its working end must be narrow enough to effectively wind the cord into the sulcus but not so sharp as to cause bleeding or perforation of the wall of the sulcus[32]. The instrument can also be double-ended, with multiple orientations of the working edge, which makes it easier to insert the cable around the tooth without having to change hand positions or tools. This design also eliminates obstructions in the field of view[33,34]. Depending on the operator's requirements, the working end can be either smooth or serrated. Smooth, rounded end devices are mainly used for packing stranded wire, while serrated end devices are used for braided wire[35]. The serrated ends prevent this cord from slipping during deployment; however, this might cause fraying if not utilised carefully. A periodontal probe can be utilised to pack interproximal cords, as gingival tissues in this location are thin and sensitive. For thin gingival biotypes, a flat plastic instrument can be used to place the retraction cord without injuring the sensitive tissue[36-39].

Single cord technique

Isolate prepared teeth with cotton rolls, use saliva evacuators as needed, and dry this field with air. Cut a string long enough to wrap around the tooth. Do not over-desiccate the tooth, as this may cause postoperative sensitivity. Soak the

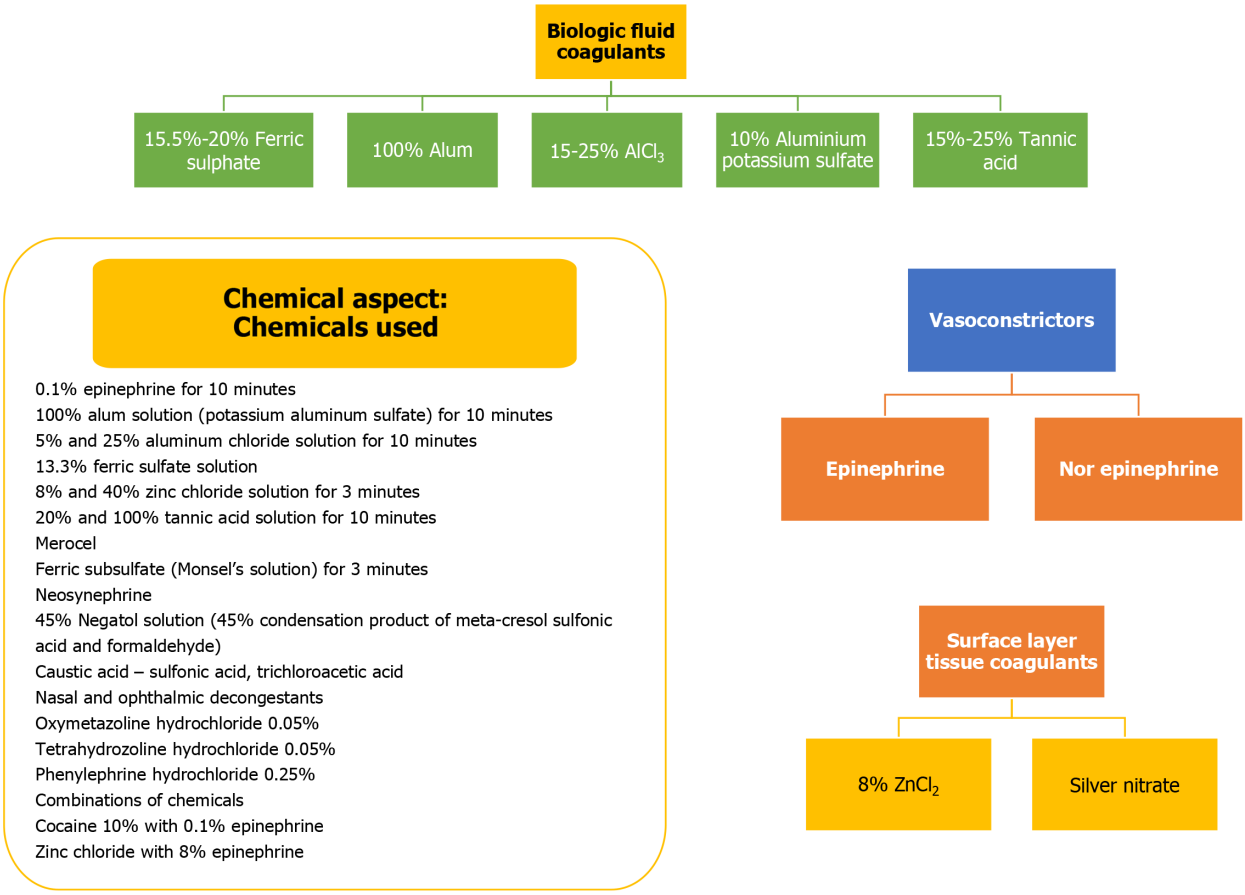


Figure 6 The chemicals used for tissue retraction.

cord in an astringent solution and remove excess with a gauze pad. To prevent the thin sulcular epithelium from sticking and ripping during removal, a wet, impregnated cord should be in place. Twist the non-braided cords tightly for easy placement. Loop the cord around the prepared tooth, forming a "U" shape. Apply low pressure in the apical direction while holding the cord between your thumb and forefinger. Starting at the interproximal area allows for easier placement of the cord compared to the facial or lingual areas. Use a Fischer packing or DE plastic device to gently slip the cord between the tooth and the gingiva in the mesial interproximal area. After tucking the cord into the mesial, use this device to lightly fasten it in the distal interproximal area. Start with the lingual surface and work from the mesiolingual corner to the distolingual corner. Move the instrument slightly toward the cord-placed location (mesial). If the instrument tip is angled away from where the cord is put, it may be dislodged and pulled out. For a shallow sulcus or finish line with shifting shapes, use a Gregg 4-5 device in the left hand to keep the cord in place[40].

To place the cord, use the packing instrument in the right hand. Use the instrument to gently press the cord apically, directing the tip slightly towards the tooth. Gently slide the cord along the preparation to the finish line. Then, push the cord into the crevice. If the instrument is aimed completely apically, the cord will bounce off the gingiva and roll out of the sulcus. If the cord continues to rebound from a narrow location of the sulcus, do not apply more force. Instead, keep a mild force for a longer duration. If the cord still rebounds, use a smaller or more malleable cord (twisted rather than braided). Secure the cord at the mesial, where it was previously lightly tacked. Cut the length of the cord extending from the mesial sulcus as close as feasible to the interdental papilla. Pack the cord around the facial surface and overlay it in the mesial interproximal area. Overlap should always be in the proximal area, where the tissue can support the excess cord. If this overlap occurs on the facial or lingual surface where the gingival is tight, there will be a gap apical to the crossing, and the finish line may not be repeated in the impression. Pack everything except the last 2.0 mm or 3.0 mm of cord. The tag is left projecting so that it can be easily gripped and removed. Tissue retraction should be forceful but gentle, ensuring the cord rests at the finish line. Do not overpack. Place a generous amount of gauze in the patient's mouth. This will make the patient more comfortable by providing something to close on while also keeping the area dry. After 10 minutes, cautiously remove the cord to prevent bleeding. Inject the impression material only if the sulcus is clean and dry. Gently remove any coagulum. Then, lightly blow air onto it. If bleeding persists, stop the impression-making procedure[40].

Double cord technique

First, a thin cord is put in and trimmed so that the ends do not overlap. A second, bigger cord is then put in and removed as usual. The thin first cord persists during the impression-making process. When incorporating this approach, clinicians should avoid damaging the epithelial connection[41].

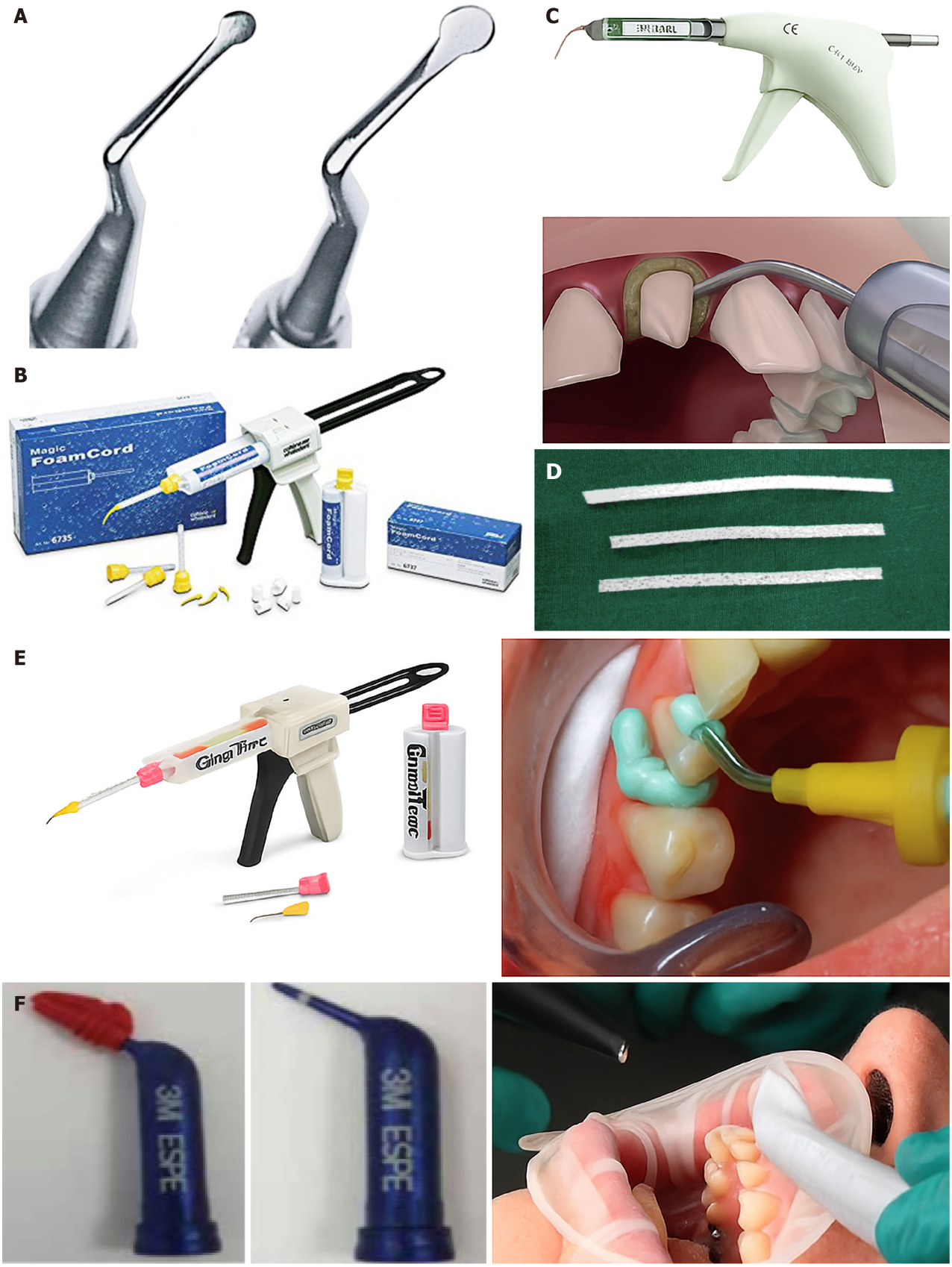


Figure 7 Instruments. A: The cord-packing instruments; B: The magic foam cord; C: The Expasyl; D: The Merocel; E: The GingiTrac; F: The retraction capsule.

Cord positioning force

Inserting the cord into the gingival sulcus requires non-damaging minimal force; otherwise, the displacement operation can result in bleeding and damage to the sulcular and junctional epithelium. Inadequate use of force during cord insertion might cause gingival recession later on due to disruption in blood flow and injury to the periodontal attachment fibres. When tucking the cord in the sulcus, considerable force may be used unintentionally, especially if the patient is anaesthetized. According to Phatale *et al*[22], the epithelial attachment sustains damage at 1 N/mm and ruptures at 2.5 N/mm, which is nearly the same force required to place the retraction cord[42].

Cord retraction time

The time the cord is placed in the gingival sulcus is also critical. If the cord is not inserted long enough, the gingival tissue may not be displaced sufficiently for the impression material to document the subgingival preparation margin. If the wire is left in place for only two minutes, the width of the gingival sulcus will be reduced to 0.1 mm within 20 seconds of removal. However, if the retractor is left in place for too long, it may lead to gum tissue damage and gingival recession. This is especially true for pre-impregnated retractors or retractors treated with hemostatic chemicals. Floss left in the gingival sulcus for an extended time may dry out. If this occurs, it can stick to the surface of the gingival sulcus and tear the surface of the gingival sulcus when removed. According to several studies, the optimal time is 1 minute to 30 minutes. The goal should be to secure the cord in the sulcus in as short a time as possible, minimising damage to the delicate soft tissues. This may be easy for single tooth preparations, but for multiple tooth preparations, it is critical to keep track of the amount of time the cord is placed on the previously prepared teeth. If it takes too long to prepare successive teeth, the cord should be removed and re-wrapped after treatment is complete. In addition, the gingival sulcus of all prepared teeth should be evaluated after the impression is taken to ensure that there are no accidental cord fragments left in the gingival sulcus[42,43].

Infusion technique

After carefully preparing cervical margins at intra-crevicular placements, bleeding is controlled with a specially designed dento-infusor containing ferric sulfate. There are two concentrations of ferric sulfate available: 15% and 20%. The 20% material is preferred over the 15% solution because it is less acidic and does not remove the smeared layer of dentin from the prepared tooth. Using a burnishing motion, the infusor is manipulated around the gingival sulcus and carried from the syringe. Once hemostasis is confirmed, a knitted retraction cord is soaked in ferric sulfate solution and inserted into the sulcus. After removing the cord and rinsing the sulcus with water, an impression is created. When using the single cord approach, the dento-infusor and 20% ferric sulfate are useful supplementary techniques for haemorrhage management. Even with a cautious procedure, isolated pockets of bleeding may occur when the cord is removed from the sulcus. In such cases, the infusion and medicament can be applied to the sulcus with hard burnishing pressure for around 15 seconds. When incorporating ferric sulfate materials, patients should be aware that their tissues may temporarily discolor. The tissues take on a blue-black hue that normally fades within a few days[41-43].

Every other tooth technique

When taking an impression of anterior teeth preparation, no damage must be done to the gingival tissues, which may result in tooth recession with root proximity; placing a retraction cord simultaneously around all prepared teeth may result in strangulation of the gingival papillae and eventual loss of the papillae. This produces unappealing black triangles in gingival embrasures. This unpleasant effect can be avoided with the "every other tooth" approach. Retraction operations are performed on anterior teeth. If teeth 5-12 are prepared, cords will be inserted around teeth 5, 7, 9, and 11. The impression is made, gingival displacement is performed on teeth 6, 8, 10, and 12, and a broad impression is created. A further pick-up impression allows the creation of a master cast, including dies for all eight prepared teeth[43].

Magic foam cord

Developed by Professor Dr. Dumfahrt, Magic foam cord is a non-hemostatic gingival retraction system manufactured by Coltène/Whaledent (Figure 7B). Made from polyvinyl siloxane, this material expands within the gingival sulcus, aiding in tissue displacement. It is used alongside a compression cap, which the patient bites down on before removal. The degree of retraction is then assessed, and if satisfactory, the final impression is taken. The system includes components such as foam, cartridges, mixing tools, intraoral tips, and Comprecaps[44].

Expasyl

Introduced by Satelec Pierre Rolland and marketed as Cordless Gingival Retraction (SDS/Kerr Company), Expasyl is a viscous synthetic slurry containing 10% aluminium chloride, 80% kaolin, water and modifiers (Figure 7C). When injected into the sulcus, it exerts gentle pressure without causing damage to the gingival tissues. The small cannula tip allows for precise placement, making the process faster and less traumatic for the patient. However, the high aluminium chloride concentration has been linked to tissue necrosis and sensitivity[45].

Merocel

Developed in 1996 by Ferrari *et al*[30], Merocel is a synthetic polymer cut into 2 mm sponge-like strips (Figure 7D). It is derived from hydroxylated polyvinyl acetate, a biocompatible material that absorbs fluids and expands within the gingival sulcus. After removal, it exposes the finish line, allowing for impression-taking. Besides dental applications, Merocel is also used in ear, nose, and throat, gastric, and otoneurosurgical procedures[46].

GingiTrac

GingiTrac is a mild natural astringent gel (Figure 7E), used alongside foam cylinders, which are available in two sizes: Regular and Large. The procedure involves placing a polyvinyl siloxane paste into the gingival sulcus and instructing the patient to bite down for 3-5 minutes to allow the material to set. The assembly is then removed, and the retraction level is evaluated. If the sulcus is adequately retracted, the final impression is made; otherwise, the process is repeated. This technique is minimally invasive and gentle on gingival tissues[45,46].

Retraction capsule

The retraction capsule (Figure 7F) contains a high-viscosity astringent paste with 15% aluminium chloride, designed for use with a composite capsule dispenser. It features a long, slender nozzle with a soft edge, allowing precise delivery into the gingival sulcus. Additionally, a white orientation ring on the nozzle matches the size and position of a periodontal probe, preventing excessive insertion and ensuring controlled application[47].

Rotary curettage or gingettage

In 1954, Amsterdam described the idea of rotary curettage. A torpedo-tipped diamond forms a chamfer finish line while also removing the sulcus' epithelial lining. It is a troughing procedure used to remove a minimal amount of epithelial tissue in the sulcus while creating a chamfer finish line in tooth size. The method known as "gingettage" is used for subgingival placement of restorative margins. Before rotary curettage, a shoulder is developed at the gingival crest. Rotational curettage should only be performed on healthy, inflammation-free tissue to minimise tissue shrinkage that occurs when diseased tissue heals. The following parameters must be met for gingettage: (1) The absence of blood when probing the gingiva; (2) The depth of the sulcus is less than 3 mm; and (3) The presence of sufficient keratinied gingiva [48].

Electro-cautery or electro-surgical retraction

Electrosurgery refers to the considerable reduction of sulcular epithelium achieved with the use of an electrode to cause gingival retraction. It is a high-frequency radio transmitter that employs a vacuum tube or a transmitter to produce an electrical current of at least 1.0 MHz (one million cycles per second). The surgery is also known as surgical diathermy[48, 49].

Lasers in gingival retraction

Recent advancements in dentistry have facilitated the use of lasers for hemostasis and soft tissue removal before impression-taking. By eliminating tissue within the gingival sulcus, lasers allow for a clear view of the preparation margins, enabling highly accurate impressions. While diode lasers are the most commonly used for this purpose, neodymium-doped yttrium aluminium garnet (Nd: YAG) and erbium-doped yttrium aluminium garnet (Er: YAG) lasers are also effective. Studies indicate that laser-assisted gingival retraction is less painful and, in some cases, can even be performed without anaesthesia[48]. Additionally, lasers minimise postoperative pain, bleeding, and gingival recession. However, they come with higher operational costs and require more time for tissue removal compared to electrocautery or a scalpel. Despite these limitations, lasers are widely employed for tissue contouring procedures[49].

Retraction around implants

The soft tissue surrounding implants differs significantly from that around natural teeth. Peri-implant tissues have weaker adherence, greater permeability, and lower regenerative capacity. As a result, they are more prone to damage and recession when subjected to retraction techniques. Furthermore, these tissues naturally tend to retract even after retraction procedures, making impression-taking particularly challenging, especially for deeply placed implants. Comparing different retraction techniques, research suggests that retraction cords may cause excessive trauma to the delicate peri-implant tissues. Instead, chemical retraction agents - such as 15% aluminium chloride in an injectable kaolin matrix - are preferable, as they cause minimal damage to the junctional epithelium. However, their effectiveness decreases when working with subgingival margins[49]. From a surgical standpoint, Nd: YAG lasers are not recommended near implants since their wavelength can overheat the implant, leading to bone damage. In contrast, the Er: YAG laser is safer because its energy is reflected by metal surfaces, but it is less effective for hemostasis compared to the CO_2 laser. Electrosurgery is also unpopular due to the risk of osteonecrosis and arcing through metal implants. Additionally, rotary curettage should be avoided, as limited tactile control may result in unintentional damage to the implant's surface. The absence of keratinized gingiva in peri-implant areas further increases the risk of tissue recession if rotary curettage is attempted[49,50].

Retraction for digital impressions

One major challenge with traditional visual impressions is the restricted line of sight, which can limit accuracy. In digital computer-aided design and computer-aided manufacturing impressions, maintaining a clear sulcus is crucial. Residual retraction cord fibres within the sulcus may compromise gingival retraction accuracy, leading to artifacts and errors in the digital impression. A 15% aluminium chloride injectable matrix is often preferred because it leaves the sulcus clean upon removal, reducing the risk of artifacts. While indirect data capture is generally considered more precise, its accuracy is influenced by the thickness of the impression material within the sulcus. If the impression margins are too narrow, especially if their radius is smaller than the contacting probe tip, this can result in significant inaccuracies[51].

CONCLUSION

As gingival traction is an essential element of clinical practice, clinicians should make every effort to use the many procedures and products of gingival tissue traction in a variety of clinical situations. Sometimes, a variety of methods is required, and certain things may work for a particular practitioner but not for another. The effort placed into proper gingival tissue retraction pays significantly in terms of restoration lifespan, margin improvement, and aesthetics.

FOOTNOTES

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MINIREVIEWS

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Abstract

Nocturia is a common clinical condition that severely affects patients' quality of life and is strongly associated with complications such as depression, cognitive dysfunction, mood disorders, and fall-related injuries. The etiology of nocturia is complex and mainly includes increased total urine output, nocturnal polyuria, decreased functional bladder capacity, sleep disorders, and confounding factors. In recent years, with the in-depth study of the pathophysiological mechanisms of nocturia, the diagnostic methods have been updated, and the application of tools such as the frequency volume chart, bladder capacity index, and bladder diary have provided an important basis for the precise identification of the etiology. Behavior modification has been widely used in clinical practice as a first-line treatment. In addition, advances in pharmacotherapy have provided new directions for the management of nocturia, and the efficacy and safety of α-blockers, cholinergic receptor antagonists, adrenergic β-agonists, desmopressin, melatonin, and other medications have been gradually validated. However, there are still some limitations in the existing studies, especially in the long-term safety and efficacy of drug therapy as well as the mechanism of action still need to be further explored. This article reviews the latest research advances in nocturia, aiming to provide clinicians with diagnostic and therapeutic strategies based on evidence-based medicine, and to promote the standardization and individualization of nocturia management.

Key Words: Nocturia; Nocturia diagnosis; Nocturia treatment; Desmopressin; Melatonin

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Core Tip: Nocturia increases the risk of death in patients. However, the pathogenesis, diagnosis and treatment of nocturia are complex. We summarize the current state-of-the-art in pathophysiology, diagnostic methods, and treatment strategies, with frequency-volume chart and bladder diaries providing an important basis for diagnosis, and more comprehensive studies of pharmacological treatments are needed in the future.

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INTRODUCTION

Nocturia is often described as the most bothersome of all urinary symptoms and one of the most common. Nocturia was defined by the International Continence Society (ICS) in 2002 as a condition in which the patient wakes up ≥ 1 time during the night to urinate and each time causes interruption of sleep[1]. Nocturia affects approximately 25% of females and 20% of males in the general population and can severely impact the quality of life (QOL) of the population. Despite the relatively low prevalence of nocturia among young adults, this phenomenon shows a tendency to increase with age. In the older age group of 60 years and older, more than 70% of individuals report problems with nocturia, with more than one-third (36%) needing to get up to urinate two or more times per night[2,3]. A recent high-quality meta-analysis suggests that nocturia may be associated with an approximately 20% increased risk of falls, a 32% increased risk of fractures, and a 1.3-fold increased risk of death[4,5]. The International Consultation on Lower Urinary Tract Symptoms (LUTS) in Men[6] classified nocturia into five categories based on its different pathophysiologic mechanisms: Increased total urine output, nocturnal polyuria (NP), decreased functional bladder capacity, sleep disorders, and mixed factors. It has a variety of potential etiologies, including physiologic and pathologic factors. Physiologic factors are usually seen in excessive nocturnal fluid intake, caffeine, alcohol, and high sodium diets; and medical disorders such as hypertension, diabetes mellitus, obstructive sleep apnea syndrome, peripheral edema, and organic changes in the urinary system are common etiologies[7,8]. This article summarizes the underlying pathophysiology of nocturia and updates a comprehensive diagnostic approach to nocturia in order to understand the etiology of the condition so that different therapeutic options can be selected.

Pathophysiology and classification of nocturia

Nocturia is a multifactorial disorder caused by different mechanisms such as increased that have been comprehensively studied in terms of pathophysiology and are categorized as follows: Increased total urine output, NP, decreased functional bladder capacity, sleep disorders and confounding factors. Exploring these mechanisms is crucial for clarifying the root causes of disease and developing precise treatment strategies, and its core content covers the following key dimensions (Figure 1).

Increased total urine output: A 24-hour urine output of more than 3000 mL (urinary rate ≥ 125 mL/h) can be caused by osmotic polydipsia or aqueous polydipsia. Osmotic polydipsia is usually accompanied by a urine osmolality > 300 mOsm/L, as in diabetes mellitus, while aqueous polydipsia manifests itself as a urine osmolality < 300 mOsm/L and is seen in uremia or excessive fluid intake. Uremia can be caused by pressor deficiency (central) or renal resistance to pressor (nephrogenic), and common causes include brain injury and tubulointerstitial disease[9].

NP: NP is defined by ICS as nocturnal urine volume (NUV) greater than 20%-33% of the 24-hour urine volume (percentage adjusted for age)[1]. This percentage is referred to as the NP index (NPI). The normal value of the NPI ranges from 14% in young people to 34% in people over 65 years of age, and thus several thresholds have been proposed. Other definitions of NP have been proposed, such as NUV > 6.4 mL/kg, NUV > 0.9 mL/min, or NUV > 90 mL/h[10,11]. Nocturia is mainly regulated by two hormones: antidiuretic hormone (pressor) and atrial natriuretic peptide (ANP). Among them, the secretion level of antidiuretic hormone is regulated by both plasma osmolality and body fluid volume, and its main physiologic function is to promote water reabsorption in the renal collecting ducts. Urine dilution may be triggered when certain pathological conditions (*e.g.*, uremia) interfere with the normal secretion of antidiuretic hormone or affect renal sensitivity to it. Pressurin secretion fluctuates naturally between day and night, with healthy individuals experiencing peaks in pressurin levels at night, whereas patients with NP lack this nocturnal elevation of pressurin. In addition, individuals who do not suffer from insomnia usually have higher levels of nocturnal melatonin secretion than insomnia patients[9,12,13]. On the other hand, disorders like obstructive sleep apnea that cause obstruction of the upper airway are able to stimulate the release of cardiac natriuretic hormone from the atria and ventricles by increasing the negative pressure in the thoracic cavity and facilitating the flow of more venous blood to the heart. ANP further exacerbates NP by inhibiting the secretion of pressurizing hormone and decreasing the reabsorption of sodium. Congestive heart failure is also a common cause of elevated ANP levels and subsequent NP[13]. In addition, diseases such as diabetes mellitus, hypoalbuminemia, venous stasis of the lower extremities, cirrhosis, and renal insufficiency can trigger peripheral edema and increase renal burden due to the transfer of fluids from the interstitium to the vasculature while the patient is at bed rest, leading to nocturia. Lifestyle factors, such as excessive intake of salt, fluids, alcohol, or

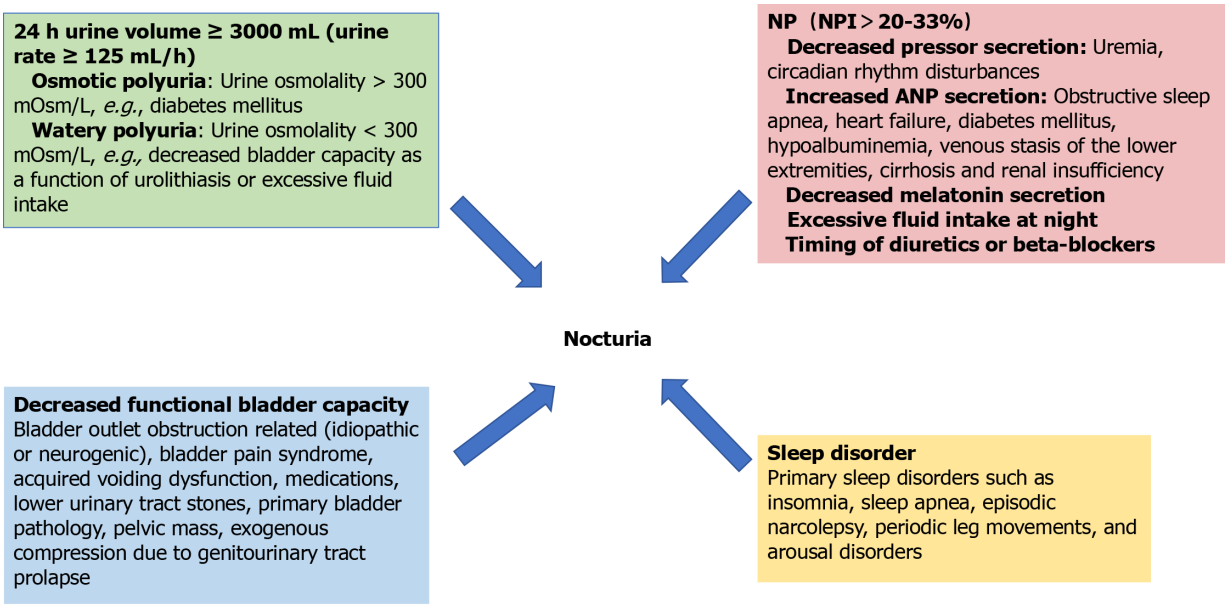


Figure 1 Aetiology of nocturia. NP: Nocturnal polyuria; NPI: Nocturnal polyuria index; ANP: Atrial natriuretic peptide.

caffeine at night, are also a common cause of NP. Finally, the timing of diuretics or beta-blockers may also influence the increase in nocturnal urine output[14].

Decreased functional bladder capacity: The reasons for this condition of the bladder are multiple: Significant postvoid residual urine due to decreased bladder contractility, usually associated with associated bladder outlet obstruction (BOO) caused by benign prostatic hyperplasia (BPH), detrusor overactivity (DO) [idiopathic (usually concurrent with BPH) or neurogenic], bladder pain syndrome, acquired voiding dysfunction, medications, lower urinary tract stones, primary bladder pathology resulting in reduced anatomical capacity, or exogenous compression due to pelvic mass or genitourinary tract prolapse[10,15,16].

Sleep disorders: Primary sleep disorders such as insomnia, sleep apnea, episodic narcolepsy, periodic leg movements, and arousal disorders can cause nocturia. Heart failure, chronic obstructive pulmonary disease (COPD), endocrine disorders, and neurological disorders can also cause sleep disorders, leading to nocturia.

Mixed factors: Including the above reasons, commonly found in the elderly, combined cardiovascular and cerebrovascular diseases and patients taking related drugs.

Diagnosis of nocturia

Nocturia requires a combination of diagnostic methods to further define the pathophysiology of nocturia in each patient, making the diagnostic approach particularly important and consisting of the following four components: History taking, physical examination, supporting diagnostic scales, and ancillary tests.

Medical history enquiry: Thorough history taking can help the clinician better determine the underlying etiology of nocturia and develop an appropriate treatment plan. The history inquiry should include several areas. First, LUTS are a key component of the nocturia workup, and nocturia frequency, daytime LUTS, and voiding rhythm should be assessed by 24-hour frequency-volume chart (FVC) or a bladder diary, during which the patient should be questioned about his or her lifestyle habits, including daily fluid intake[17], alcohol intake, caffeine intake (especially at night or near bedtime), dietary sodium intake[18] and the presence of sleep disorders. The high prevalence of nocturia in the elderly population is closely related to a variety of underlying diseases and long-term medication use. There are various etiologies that trigger nocturia symptoms, such as cardiovascular diseases (congestive heart failure), respiratory diseases (obstructive sleep apnea, asthma, COPD), endocrine-metabolic diseases (diabetes mellitus, thyroid dysfunction), neurological disorders (Parkinson's disease, dementia), genitourinary disorders (uterine prolapse), and other sleep-related disorders (rapid eye movements, sleep behavior disorders, restless legs syndrome, episodic sleep disorders)[16]. In addition, disturbances in the secretion of key hormones that regulate fluid and electrolyte balance (*e.g.*, antidiuretic hormone and ANP) can lead to NP[19,20]. In terms of pharmacologic factors, medications that may cause fluid retention (*e.g.*, nonsteroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers, glucocorticoids, thiazolidinediones hypoglycemic agents, pramipexole, and gabapentin), as well as diuretics taken at bedtime, may induce or exacerbate nocturia symptoms.

Physical examination: In addition to routine checkups, the consensus recommends focusing on the following examinations, such as weight, waist circumference and blood pressure; cardiac and respiratory examinations; foot and ankle

examination of the lower extremities for edema; palpation of the suprapubic area for urinary retention; rectal examination of the prostate gland for male patients, and pelvic floor examination of the pelvic floor for uterine prolapse and other gynecological disorders for female patients.

Auxiliary diagnostic scales

As an important tool for the diagnosis of nocturia, 24-hour FVC measures and records the volume and time of each urination during the day and night for 3 consecutive days, combined with the following parameters:

NUV: The total amount of urine voided each night, including the first urination in the morning.

Nocturnal urine output: From the time you go to sleep to the time you wake up in the morning; the first morning urination is not counted as nocturnal urine output.

NPI: Which refers to the proportion of nocturnal urine output in 24-hour urine output, NPI = NUV/24 h urine output × 100%.

Nocturia index: The proportion of nocturnal urine output to maximum urine output, Nocturia index (Ni) = nocturnal urine output/maximum urine output.

Predicted number of nocturnal voids: Predicted number of nocturnal voids (PNV) = Ni-1; actual number of nocturnal voids (ANV).

Nocturnal bladder capacity index: Nocturnal bladder capacity index (NBCI) = ANV-PNV.

Polyuria was diagnosed when the 24-h urine volume was > 40 mL/kg; NP was diagnosed when NP was > 33% (≥ 65 years), > 25% (> 35 years and < 65 years), or > 20% (≤ 35 years); and nocturnal bladder capacity reduction was diagnosed if the NUV was less than the maximal bladder capacity, and diagnosis was made by applying NBCI. When ANV exceeds PNV, an NBCI > 0 indicates reduced nocturnal bladder capacity relative to the patient's maximum 24-hour capacity[21,22]. Patients who meet the criteria for polyuria should be identified with volumetric polydipsia (*e.g.*, diabetes mellitus) or urolithiasis. Patients with suspected sleep disorders should undergo further sleep-related examinations, such as sleep duration, nighttime wakefulness, nighttime sleep quality, the time of the first sleep cycle (the time between sleep and the first awakening to urinate), and other special examinations such as sleep electroencephalography, *etc.*, if necessary.

In addition, the Overactive bladder Symptom Score (OABSS) and the International Prostate Symptom Score (IPSS) were used to assess concomitant LUTS in patients with nocturia; QOL was assessed using the Perceived Bladder Condition Scale (PPBC), the Nocturia QOL Questionnaire, and the International Counseling Incontinence Questionnaire; and sleep disorders were assessed with the Berlin Questionnaire Survey, the First Uninterrupted Sleep Period (FUSP) questionnaire[21,23]. FUSP questionnaire to assess sleep disorders[21,23], and sleep polysomnography to assist in the diagnosis of sleep-related disorders such as obstructive sleep apnea.

Auxiliary examination

Laboratory tests: On the basis of routine tests (urine routine, urine culture, liver and kidney function, blood glucose, blood electrolytes), monitor changes in blood and urine osmolality. Normal human plasma arginine vasopressin is 2.3-7.4 pmol/L.

Imaging: Ultrasonography of the urinary tract is preferred, and CT and/or magnetic resonance imaging (MRI) of the urinary tract may be performed if the results are abnormal. Voiding cystourethrography can be used to assist in the diagnosis of primary bladder neck obstruction, but is not suitable for assessing the severity of urinary symptoms[24]. MRI of the head may assist in the diagnosis of urolithiasis secondary to neurological disorders such as suprasellar tumors. Cardiovascular ultrasound can assist in the diagnosis of cardiovascular disease, such as nocturia due to congestive heart failure.

Urological examination: for those who have difficulty in urination, urinary flow rate, residual urine and other tests, invasive urodynamic examination if necessary, and cystoscopy if necessary to exclude bladder tumors or stones and other organic lesions.

The latest European Association of Urology (EAU) guidelines on non-neurogenic LUTS state that in the diagnosis of nocturia in men[25] a detailed history is mandatory, a bladder diary or FVC is particularly helpful, followed by a review of behavioral factors affecting fluids and sleep, and a detailed questioning of the patient's history of other illnesses and medications, which states that the IPSS is an assessment of the comprehensive range of symptoms of the prostate, and that although the questionnaires are well established and widely used in urology, the limitation is his inability to accurately assess the distress caused by each individual symptom, including nocturia. The EAU guidelines recommend the use of validated symptom-scoring questionnaires, and a number of questionnaires that are sensitive to symptomatic changes have been developed and can be used to monitor treatment. Symptom scores help to quantify LUTS. In diagnosing nocturia in women[26], a thorough medical history is an integral part of the assessment of women with nocturia, including screening for sleep disturbances. In addition to a bladder diary, tests for renal function, thyroid function, glycosylated hemoglobin, and serum calcium levels need to be considered.

The latest ICS guidelines point to the following diagnostic strategies[17]: bladder diary consensus, but there is no

consensus at the moment on its duration (3 days is recommended). Diary consensus on sleep, intake (fluids and food), and physical activity, the need to check blood pressure and edema, and, if necessary, PSA, serum sodium screening (SSC), renal/cardiac function and endocrine screening, as well as pelvic (in women) or rectal examination (in men) screening, the timing or fasting at the time of the SSC execution does not matter. The ICS guideline also proposes a widely used and validated patient-completed questionnaire, the International Consultation on Urinary Incontinence Questionnaire for Men with LUTS, which includes incontinence problems and disturbs for each symptom. It contains 13 items, including subscales for nocturia and OAB.

Diagnosis and differential diagnosis of nocturia is very important and more and more questionnaires and diagnostic methods are being proposed, FVC, bladder diary of 3 days and more, factors affecting fluids and sleep, history of disease and medication history reached consensus but questionnaires did not, this is a direction for further research in the future.

TREATMENT AND MANAGEMENT STRATEGIES FOR NOCTURIA

Based on the specific pathophysiology of nocturia in each patient, appropriate treatments are required to achieve effective relief of nocturia, and there is growing evidence of the effectiveness of pharmacological treatments in addition to lifestyle guidance and behavioral treatments, with the current status of treatments for each of the different interventions indicated below.

Lifestyle guidance and behavioral therapy

Drinking water related guidance: The first line of treatment to change urinary symptoms is recommended to be behavioral therapy, focusing on suspected underlying causes. Lifestyle changes are important, including limiting fluid intake: About 100 ounces of fluid per day for healthy men and 70 ounces per day for women. Fluid intake varies by age, with 45 to 60 ounces of caffeine-free beverages per day recommended for older adults. It is recommended that daily fluid intake should be rationally distributed throughout the day and strictly controlled within 3-4 hours before bedtime, with a particular need to avoid alcoholic and caffeinated beverages. In terms of lifestyle and dietary management, a healthy dietary pattern is recommended, in which daily sodium intake should be limited to 8 grams[27,28]. In non-randomized controlled trial (RCT) studies, high dietary sodium intake increased nocturia[29], which was further supported by observations from an observational study[18]. High dietary intake of fruits and vegetables was shown to be associated with nocturia, while high intake of tea was associated with nocturia in observational studies. In patients with leg edema, wearing compression stockings and leg elevation before going to bed can reduce edema, which in turn reduces nocturnal fluid flow and thus NP[30]. Sleep-related modifications can also help to manage urinary symptoms, as shown in a recent RCT of sleep behavioral interventions for patients with nocturia[31]. Over the 14-day assessment period, total nocturnal urination decreased by 6.5 ± 4.8 in the brief behavioral therapy for insomnia (BBTI) group and increased by 1.3 ± 7.3 in the information control (IC) group (P = 0.04, effect size 0.82), which suggests that patients follow the principles of BBTI for insomnia, which include reducing bedtime, waking up at the same time each day, going to bed only when sleepy, and staying in bed only when asleep.

Exercise therapy: Pelvic floor muscle function training as a non-pharmacological intervention can effectively improve the related symptoms. The specific training method is as follows: patients are instructed to consciously contract the pelvic floor muscle groups while relaxing the abdominal muscle groups for 2-10 seconds each time, and the total number of daily training is not less than 45 times. As the training continues, the duration of each contraction should be gradually extended[32]. Exercising the pelvic floor muscles may strengthen urethral control on the one hand, and also contribute to the reestablishment of inhibitory neural pathways during the storage phase, which in turn improves urinary frequency and urgency symptoms.

There are few RCTs of behavioral measures for nocturia as a primary outcome. Lifestyle-based guidance and behavioral treatments do not involve the use of medications and have no side effects on humans, and more behavioral treatments for nocturia need to be invested in clinical studies for nocturia in the future in order to provide sufficient evidence for it.

Treatment of BOO

Some studies have shown that the most common etiology causing BOO in men is prostate obstruction caused by BPH[33], which causes a series of LUTS, and nocturia is a part of its LUTS, and its treatment options have been recommended by domestic and international guidelines or consensus[34], regarding the pharmacological treatment of BPH-related nocturia in men with BPH However, the latest guidelines or consensus at home and abroad list α1 receptor blockers as first-line or preferred drugs, which can be used alone or in combination with 5α-reductase inhibitors, but their common adverse effects (postural hypotension) are prone to cause falls in the elderly and even induce cardiovascular and cerebral vascular events, and highly selective α-blockers (*e.g.*, tamsulosin) have a weak affinity for the α1B receptor, and compared with other α1-blocking agents, the incidence of hypotension related adverse effects have a lower incidence and a relatively high safety profile[33]. However, a high-quality meta-analysis by the EAU[34] pointed out that the evidence for alpha1 receptor blockers in the treatment of nocturia derived from the majority of clinical studies that included nocturia as a secondary outcome while failing to identify and exclude patients with coexisting NPs was not sufficient. Patients with BPH who have moderate to severe LUTS and have significantly affected their QOL may choose surgery and minimally invasive treatment, especially those who have poor results from medication or who refuse to accept medication, and refer

to the relevant Western medical guidelines for the surgical approach, among others.

Treatment of OAB syndrome

OAB is defined as a syndrome of storage symptoms characterized by urinary urgency, with or without urge incontinence, with frequent nocturia, the etiology of which is unclear, and although all theories relate to the term "DO", not all patients with OAB suffer from DO, which has been confirmed in only about 50% of cases[35].

Currently, cholinergic receptor antagonists and adrenergic beta agonists are still the mainstay of first-line pharmacological treatment. Cholinergic receptor antagonists (tolterodine, solifenacin) have been shown to significantly improve symptoms and QOL, but the main problem with these drugs is that the muscarinic receptors on which they act are found in many of the organs of the body, which leads to the occurrence of many common side effects: Dryness of the mucous membranes (dry mouth, eyes , vaginal dryness), constipation, palpitations, arrhythmias, tachycardia and cognitive disturbances (somnolence, hallucinations, confusion, delirium, blurred vision, memory problems) or urinary retention [36], which leads to poor compliance and inability of patients to regulate their treatment in the long term. Of the three β-adrenergic receptors present in the bladder, findings have shown that β3 is the main one and is responsible for the relaxation of the forcing muscle during the filling phase[36,37]. β3 receptor agonists (mirabolone) are comparable in effectiveness to anti-muscarinic drugs, but have fewer side effects, resulting in greater patient compliance, and in patients refractory to monotherapy, cholinergic receptor antagonists may be used in conjunction with mirabolone, with outcomes superior to those of monotherapy[35,38].

For refractory OAB (where behavioral control combined with pharmacotherapy is ineffective), intravesical injection of botulinum toxin type A (OBTA) temporary bladder detrusor chemical denervation, posterior tibial nerve stimulation (PTNS), and Sacral Nerve Stimulation (SNS) are often used, all three of which have been approved by the Food and Drug Administration in 2013, 2005, and 1997, and also recommended by ICS for SNS and transcutaneous electrical nerve stimulation as second-line treatment options for refractory OAB. However, while OBTA improves OAB symptoms, the risk of increased postvoid residual urine volume and symptomatic urinary retention, clean intermittent self-catheterization with urinary tract infections is significant[39-41], and questions remain regarding optimal administration of botulinum toxin A in OAB patients as well as post-treatment tolerability[39,40]. Neurostimulation modulation therapies such as PTNS and SNS have been a validated and widely used treatment option for lower urinary tract dysfunction for decades, and a wearable, smartphone-controlled, rechargeable percutaneous tibial nerve stimulation (TTNS) device has emerged in recent years, which offers a more convenient and easier-to-maintain treatment modality for patients with OAB[42,43]. Currently available nerve stimulation techniques vary from very low invasive treatments to more highly invasive treatments requiring delicate surgery. Some experimental techniques look promising, but follow-up studies in larger cohorts to determine efficacy are lacking. The high incidence of treatment-related adverse events (AEs) has prevented their wider use[39,40,44,45].

In terms of surgical treatment, some studies have reported treating OAB by surgery, and the main surgical modalities include bladder enlargement, bladder denervation control, forced urethrotomy, and even total cystectomy. However, due to the permanent damage caused by surgery, its long-term outcome and complications are of concern. Therefore, surgical approaches should be used with caution and should only be considered in patients with OAB who have failed to respond to all of the above.

Treatment with desmopressin

Desmopressin acetate has been widely used in the treatment of urosepsis and nocturia since its introduction to the market in 1974, and it is a human-synthesized antidiuretic hormone analog commonly used in clinical practice, and a large number of clinical studies have demonstrated the efficacy of desmopressin acetate in the treatment of nocturia[46]. Antidiuretic hormone regulates the total fluid volume and osmotic balance in the body. Elevated plasma osmolality stimulates the pituitary gland to secrete arginine antidiuretic hormone, which promotes renal reabsorption of water and reduces urine output. Desmopressin can mimic the binding of arginine antidiuretic hormone to V2 receptors on the distal renal collecting tubules to concentrate urine and reduce total urine output[47]. Although many clinical studies have demonstrated that desmopressin is effective in reducing the severity of nocturia while improving patients' QOL. A new formulation suggests that a minimum dose of 25 μg of oral sublingual desmopressin appears to be ideal for women, while men usually benefit from at least 50 μg[48]. However, the safety of desmopressin is critical to its clinical use. Only a few clinical trials of long-term use of desmopressin have been reported[49-51], and it is noteworthy that the drug is also associated with a variety of adverse effects such as abdominal pain, headache, insomnia, and hyponatremia. Among them, hyponatremia is the only serious complication associated with the drug, and the risk of hyponatremia increases with age. The conclusions of these long-term clinical studies are inconsistent, and the incidence of adverse reactions varies significantly. The occurrence of adverse reactions is mostly related to the patient's age, gender, basal blood sodium concentration, renal functional status, hemoglobin level, and cardiac functional status[52].

Female, elderly patients with low basal sodium concentration have a higher incidence of hyponatremia and should be used with caution[47]. Early monitoring of blood sodium concentration is recommended, starting on the third day of administration, once a week for 2 weeks, and then periodically reviewed every 1-2 months; if the blood sodium concentration is lower than the range of normal values, it is recommended that the drug be discontinued, and most of the adverse effects can be alleviated or disappeared on their own after the discontinuation of the drug[50,53]. Between the high sustained use of desmopressin as well as its efficacy, adjusting the dosage according to the patient's gender and age in the clinic may improve the therapeutic window and minimize the risk of hyponatremia without compromising clinical efficacy. Additional long-term safety studies of desmopressin in patients with nocturia of different ages and gender are still lacking.

Melatonin

Melatonin, as an endogenous hormone, is mainly secreted by the pineal gland and is able to regulate circadian rhythms and the sleep-wake cycle. Melatonin secretion is increased in darkness and inhibited by light, a process regulated by the supraoptic nucleus of the hypothalamus[54]. In recent years, studies on melatonin in the treatment of nocturia have gradually increased. Animal model studies have shown that melatonin, as an endogenous hormone, has an inhibitory effect on the contractility of mammalian bladder smooth muscle[55], as well as improves nocturnal bladder capacity and reduces nocturnal urine output[56,57]; however, melatonin may have different effects on humans and animals, and there are now a growing number of clinical trials that demonstrate that 2 mg melatonin is a safe and effective therapeutic method[58-60], especially in BPH, women and elderly patients. only by reducing the number of nocturnal voiding episodes without affecting bladder capacity or nocturnal urine output. In addition, nocturnal serum melatonin levels are lower in older adults with nocturia than in those without nocturia[61]. Documented side effects include decreased body temperature, sedation, dizziness and headache, depression, tachycardia, and pruritus[58].

Melatonin has been shown to be effective in the treatment of nocturia, but the therapeutic mechanism is not clear, and the following studies are available: (1) Melatonin increases bladder capacity and reduces urine output *via* γ-aminobutyric acid A receptors in the brain[61]; (2) Inhibitory effects on contractility of the detrusor muscle (directly through intracellular mechanisms)[62-65]; (3) Inhibitory effect on bladder afferents (*via* MT2 receptors expressed on the bladder of low-threshold stretch-sensitive muscle mucosa)[64]; (4) Prevention of age-related changes in bladder contractility due to its potent antioxidant effects[65]. More studies in animals are needed to fully validate the proposed multiple mechanisms of action of melatonin to ameliorate nocturia.

Traditional Chinese medicine

Currently, due to the limited efficacy, low durability, and high incidence of AE of OAB treatments, clinicians in Asia commonly use traditional Chinese medicine as an alternative to OAB treatment, such as acupuncture and acupressure. In recent years, more and more clinical studies and experimental data have supported the effectiveness of traditional Chinese medicine in the treatment of OAB. Some modern studies have shown that acupoint patches can be more effective in relieving OAB symptoms, with significant effects in improving the OABSS, Urinary Urgency Severity Scale, and PPBC [66,67]. Meanwhile, the side effects of acupressure are relatively small and can be used in combination with western medicines to achieve better therapeutic effects. Tang *et al*[67] showed that cinnamon (Cinnamomum cassia) and cinnamaldehyde, the main components of acupressure, inhibited the inflammatory and fibrotic signals in cyclophosphamide-induced OAB disease in mice. Shen *et al*[68] pointed out that electroacupuncture, whose mechanism is similar to that of SNM, can be utilized to assess the therapeutic effects of SNM, thus providing a reference for patients and clinicians to determine whether SNM treatment is effective. Although these studies did not use nocturia symptoms as the primary endpoint, they provide a new strategy for clinical treatment of nocturia.

Other medication

Some studies have shown that diuretics can be used as a second-line treatment option for nocturia. Diuretics have an onset of effect at 2 h after administration, peak at 4-6 hour, and last for 6-12 hour[69] Commonly used diuretics include hydrochlorothiazide and furosemide, which are recommended for use in the morning. NSAIDs are effective in the treatment of patients with refractory nocturia associated with BPH[70], commonly used NSAIDs include celecoxib and loxoprofen. Studies on the use of these drugs in the treatment of nocturia are few and far between, and more research is needed to prove their efficacy and safety.

CONCLUSION

Nocturia has been comprehensively studied as a pathological condition that severely affects patients' QOL, and its management strategy depends on the underlying mechanisms. Currently, with more exploration of the pathogenesis of nocturia, the multifactorial etiology of nocturia is becoming clearer, and the different etiologies require the selection of appropriate treatments to improve the patient's condition faster and better, which suggests the need for standard diagnostic strategies, which are not currently available, except for detailed history taking, bladder diaries, FVC, factors affecting fluids and sleep, history of illness, and history of medications, which have reached a consensus in all modern guidelines , neither the choice of questionnaire nor other diagnostic strategies have reached consensus. Behavior modification remains the first line of treatment, pharmacological modalities are becoming more abundant, but pharmacological treatments are associated with adverse effects and a lack of extensive long-term clinical trials; the increased risk of hyponatremia associated with desmopressin has been debated; the evidence for the effectiveness of melatonin is becoming more extensive but still lacks a clear mechanism of action; and more advanced therapeutic techniques, such as TTNS, are appearing for BOO and OAB in addition to initial pharmacological treatments. technologies, such as TTNS, which require future follow-up studies in larger cohorts to determine efficacy; the better efficacy and fewer adverse effects of Chinese medicine in the treatment of OAB are its strengths, such as acupressure and electro-acupuncture, but there is less evidence of its clinical efficacy and the mechanism of action is unclear, further evidence is needed. Although the treatment modalities are not comprehensive enough, this provides a large number of directions for individualized therapeutic management. Our goal is to make it easier for clinicians to diagnose and treat nocturia and to shorten the nocturia journey for patients. Further research is necessary to reach a consensus on diagnostic and treatment algorithms for nocturia based on underlying mechanisms, to standardize the diagnosis and to improve the management of nocturia.

FOOTNOTES

Author contributions: Hou XY contributed to conceptualization, writing–original draft; Zhang L contributed to writing–review and editing; Zhang ZJ contributed to supervision; Xu W contributed to investigation; Ye LW contributed to data curation; Zhao HY contributed to visualization, software; Suo XH contributed to resources; Hong AJ contributed to project administration. All authors have read and approved the final manuscript.

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MINIREVIEWS

Scarred and complex colorectal polyps: Traditional techniques and emerging alternatives

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Abstract

Colorectal polyps remain a significant health concern because they can develop into cancer. Therefore, accurate assessment and diagnosis of polyps, along with appropriate treatment decisions, are crucial in preventing complications or malignant transformation. Some polyps are classified as complex polyps, which means they fail to elevate due to a scar from a previously removed polyp or can be determined by a scoring system like the size/morphology/site/access score, which considers factors like site, morphology, size, and access. Management of complex colorectal polyps involves various options, including endoscopic and surgical approaches. Endoscopic mucosal resection (EMR) may be challenging in scarred polyps, as inadequate lifting can result in incomplete resection or recurrence. As a more advanced alternative, endoscopic submucosal dissection (ESD) is suitable for larger lesions, enabling *en-bloc* resection even in complex cases with EMR. However, ESD requires expertise and is more time-consuming than EMR, often necessitating hospitalization due to its complexity. Endoscopic full-thickness resection could be a viable alternative for managing scarred polyps. Endoscopic powered resection, either alone or in combination with other modalities, can also be used to achieve less extensive resection. Managing complications during the procedure or post-procedurally is equally important, as bleeding or perforations can be fatal. Careful patient selection based on individual profiles and risk factors, along with the identification of any signs of malignancy, is crucial before treatment to avoid negative post-treatment outcomes.

Key Words: Colorectal polyps; Scarred polyps; Recurrence; Endoscopic mucosal resection; Endoscopic full-thickness resection; Endoscopic powered resection; EndoRotor

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Core Tip: Scarred and complex colorectal polyps remains a big concern because of fibrosis, technical complexity, and excessive recurrence rates. Traditional endoscopic techniques, which includes endoscopic mucosal resection, can be useless in these instances. Emerging alternatives, inclusive of endoscopic submucosal dissection, endoscopic full-thickness resection, and endoscopic powered resection, offer promising solutions for *en-bloc* resection and lowering recurrence rates. A multidisciplinary technique, integrating high imaging, and different resection techniques, is vital for optimizing affected person results and minimizing complications.·

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INTRODUCTION

Colorectal polyps are gastrointestinal polyps defined as abnormal growths that protrude in the lumens of the colon or rectum and are often discovered during colonoscopies. There are various types of polyps; they differ in size, morphology, and histological characteristics. The size and morphology of the polyps define the modality of management. In addition, the histological classification of polyps determines the follow-up plan, as described by Bujanda *et al*[1].

As explained in Repici *et al*[2] and Longcroft-Wheaton *et al*[3], most detected polyps during screening colonoscopies are small, benign, and easily managed endoscopically. However, around 10%-15% of colorectal polyps are classified as "complex". Recent studies fail to make a clear differentiation between complicated polyps and scarred polyps. The WEO Consensus on Colorectal Lesions Classification describe complex polyps relied on certain characteristics, such as location, size (> 2 cm), and surface characteristics that make endoscopic removal hard. Scarred polyps distinguished by submucosal fibrosis, which might be due previous procedurues such as partial resections or biopsies. While complex polyps may need progressive resection techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), scarred polyps commonly need specific techniques to overcome fibrosis, such as traction techniques or full-thickness resection (EFTR). The word complex reflects the varying degrees of complexity in size, shape, extent, location, and scarring contributing ultimately to the resection complexity using conventional endoscopic methods. Complex polyps are generally defined as any lesion whose endoscopic resection is technically difficult because of its (1) size (> 20 mm); (2) morphology (sessile); (3) extent (polyps occupying greater than a third of the lumen circumference, wrapping a fold (clam-shell polyps), and polyps crossing over two haustral folds); (4) location (right side, ileocecal valve, appendiceal orifice, sigmoid colon, dentate line, and inner curve of hepatic and splenic flexures); or (5) presence of inflammatory bowel, disease (IBD), diverticulosis, strictures, or scarred polyps from previous biopsy or failed polypectomy as shown in Vormbrock *et al*[4], Jung *et al*[5], Sanchez-Yague *et al*[6], Hintze *et al*[7], Iishi *et al*[8], Waye *et al*[9] and Mönkemüller *et al*[10]. Technical difficulty can be assessed *via* the size/morphology/site/access (SMSA) scoring system, which helps predict the risk of incomplete resection, adverse events, and recurrence based on the scoring system (Table 1), prescribed by Sansone *et al*[11] and Sidhu *et al*[12]. Over the past decade, numerous attempts have been made to manage nearly all types of colorectal polyps including polyps with local invasive carcinoma. Baker *et al*[13] descriped different endoscopic techniques for managing scarred and complex polyps include EMR and submucosal ESD. These methods have an important role, especially when polyps are contained within the mucosa with no lymph nodal involvement. In situations where traditional endoscopic approaches fail in treating scarred polyps, more advanced techniques such as EFTR are used. In addition, innovative devices such as Zaghloul *et al*[14] introduced EndoRotor, which show a solution using endoscopic powered resection (EPR), which is a non-thermal device that provides a safe and effective alternative for removing scarred polyps with a success rate of 84% with minimal complications. The early resection of polyps including scarred polyps could prevent colorectal cancer. These polyps have a high recurrence rate, highlighting the importance of diagnostic and post-endoscopic resection surveillance strategies. Kandiah *et al*[15] emphasized that, managing scarred and complex polyps is challenging due to technical complexity and the high risk of complications. Usually managing them requires skilled endoscopists equipped with the necessary tools. The current advances in research and endoscopic techniques and technologies provide tools to ensure effective treatment while prioritizing patient safety. This review aimed to discuss the types, diagnosis, and management of scarred and complex colorectal polyps. Additionally, despite the fast progress of endoscopic technologies, recent studies on cutting-edge techniques as artificial intelligence (AI)-assisted classification and molecular imaging still understated in the current literature. Combining these advancements is crucial for diagnostic accuracy and therapeutic strategies.

Numerous unresolved concerns persevere despite significant advancements have been made in the management of scarred polyps. One key gap is the lack of a comprehensive, systematic approach adding multimodal treatment pathways for these lesions. This review aims to bond this gap by explaining the first organized integration of different therapeutic decisions and presenting decision-making framework relay on the SMSA-Scar Index.

Classification of polyps

According to D'Amico *et al*[16], Burgess *et al*[17], Nusko *et al*[18], and Myung *et al*[19], the first step in polyps' classification is the endoscopic assessment of the lesion with high-definition white light imaging. This allows the evaluation of

Table 1 Size, morphology, site, access scoring Four polyp levels (with increasing level of complexity) were identified based on the range of expert scores obtained

Factor	Benchmarks	Points
Size	< 1 cm	1
	1–1.9 cm	3
	2–2.9 cm	5
	3–3.9 cm	7
	> 4 cm	9
Morphology	Pedunculated	1
	Sessile	2
	Flat	3
Site	Left	1
	Right	2
Access	Easy	1
	Difficult	3

Level 1 (4-5), level 2 (6-9), level 3 (10-12) and level 4 (> 12).

fold convergence, edge retraction, expansion/thickened folds, firm consistency, and erythema. However, the assessment of submucosal invasive cancer risk appears to be associated with increasing size, recto-sigmoid location, and surface morphology. A basic polyps classification is the lateral spreading lesions (LSL) classification. LSL classification generally classifies polyps as: (1) Granular Lateral spreading lesions (G-LSL), representing polyps that spread laterally and circumferentially rather than vertically; (2) Granular lateral spreading lesion with dominant nodule (G-LSL with dominant nodule); and (3) Non-granular lateral spreading lesion.

Non-lifting polyps including polyps with fibrosis or scarring

The difference between non-lifting polyps and scarred polyps is often neglected, leading to ineffective treatment strategies. Scarred polyps mainly occur due to submucosal fibrosis arising from prior events like biopsies, partial resections, or ablative therapy. As the changed tissue compliance caused by this fibrosis, traditional lifting techniques are less effective. Nevertheless, not every polyp that does not lift is scarred. Other causes of non-lifting behaviour contain deep invasive cancer, submucosal tumours (like lipomas or carcinoids), or inadequate submucosal injection. It is critical to differentiate between these causes since submucosal tumours might require different diagnostic and treatment approaches, such as endoscopic ultrasound (EUS) evaluation before resection, however fibrotic polyps may advantage from techniques such as EFTR or hybrid ESD. Non-lifting polyps are characterized by failure of elevation after injecting the submucosa, leading to failure of resection using endoscopic techniques, making the management a bit complicated. Due to submucosal fibrosis presenting with non-elevating polyps leading to lack of elevation during the procedure, methods such as EMR may fail to successfully manage these polyps completely, as explained in Friedland *et al*[20]. However, EPR using EndoRoto is recommended to treat non-lifting scarred polyps.

Polyps with fibrosis or scars often result from prior failed attempts of resection or less likely biopsies, leading to anchored bases with failure to elevate after injecting the base, making them less suitable for conventional endoscopic techniques There are different types of fibrosis mainly primary fibrosis, which is commonly linked to chronic inflammatory diseases like Crohn's disease or ulcerative colitis and occurs without any prior endoscopic or surgical procedures. Other forms of fibrosis can cause scarred polyps, which alters the causes and approaches of treatment. It may be essential to establish combine therapeutic treatment like biologics or anti-fibrotic drugs with specific endoscopic techniques to heal inflammatory-driven fibrosis. EMR, ESD, or surgery are samples of prior procedures that can result in secondary fibrosis. Due to the dense submucosal scarring, these lesions are usually challenging to eliminate endoscopically, require specific procedures such EFTR, traction-assisted ESD, or hybrid resection approaches as mentioned in Ayoub *et al*[21]. Ichkhanian *et al*[22] noted that, this lack of elevation could also lead to difficulty in containing the polyp in the polypectomy snare either in hot polypectomy, cold polypectomy, or EMR techniques, thus increasing the risk of diathermy-induced perforation. Ichkhanian *et al*[22] reported that, fibrosis increases the risk of adverse events during resection in general and is linked with high rates of recurrence ranging from 10-20% post-resection. Moreover, incomplete removal of these scarred polyps can elevate the risk of colon cancer.

Large sessile polyps

Hao *et al*[23] highlighted that, large polyps more than 20 mm in size can be flat or bulky in appearance, frequently extending across multiple haustral folds and in a large portion of lumen circumference. Managing these polyps is challenging due to their bulky nature and extent. Moreover, the difficulty in managing sessile polyps increases when

these large polyps are present in certain areas such as the right side of the colon, ileocecal valve, or near the dentate line. Sessile and flat polyps should also be classified as granular (homogeneous or nodular-mixed) or non-granular (elevated or pseudodepressed), as these two different types are associated with certain risks of submucosal invasive cancer (SMIC). The SMIC risk was found to be higher in polyps of nongranular pseudodepressed nature, followed by polyps of granular nodular-mixed nature, then polyps with nongranular flat-elevated nature, and at last come granular-homogeneous types.

Integration between the scarred polyp classification and treatment approaches can improve clinical decision-making. For Low-Fibrosis Polyps (SMSA Score < 8, Minimal Scarring) EMR with submucosal lifting is the favoured technique. Cold snare resection may be beneficial for smaller lesions (Partial Submucosal Fibrosis, SMSA Score 8–10) Moderate-Fibrosis Polyps Traction-assisted ESD or hybrid ESD (ESD-assisted EMR) are the chosen approaches. Also if lifting still feasible Piecemeal EMR can be done. If restricted to superficial layers, EFTR (Endoscopic Full-Thickness Resection) is the favoured technique for high-fibrosis polyps (severe submucosal fibrosis, SMSA Score > 10). Other substitutes contain laparoscopic-assisted endoscopic resection for challenging colonic locations, like the flexures or right-sided colon.

Diagnostic evaluation

Recently, to aid in diagnosing invasive lesions, the United States Multi-Society Task Force guidelines recommend a second step of assessment using aids such as the Paris classification, and virtual chromoendoscopy (such as Narrow Band Imaging, or chromoendoscopy).

Axon *et al*[24] described that, Paris classification takes the polyps' morphology into focus, classifying polyps as protruding (0-Is—sessile, 0-Ip—pedunculated, and Isp—semi-pedunculated), flat (elevated 0-IIa, flat 0-IIb, and depressed 0-IIc) and excavated (Type 0-III). Excavated lesions are rarely seen in the colon. Depressed lesions have an increased risk of malignancy (30%–50% of cases). Recent researches highlighted the elevated malignancy risk linked to depressed-type colorectal lesions, mainly those showing asymmetrical surface patterns and Kudo pit pattern type V. Regarding recent ESGE guidelines (2024), risk factors comprise Irregular or interrupted vascular construction on narrow-band imaging (NBI), occurrence of deep submucosal invasion (SM3 or beyond) relyed on high-resolution magnification endoscopy, eventually histological features like high-grade dysplasia or initial submucosal carcinoma. AI models can improve real-time estimation of malignancy possibility in depressed-type lesions, enhancing sensitivity while preserving specificity. Integrating these risk stratification tools can significantly affect management choices, guiding the choice of *en bloc* resection *via* ESD against early surgical intervention when deep invasion is supposed.

Helpful endoscopic tools

Complex and scarred polyps are usually diagnosed in endoscopic procedures. This could be done with the help of some extra functions integrated into the processor or aids such as dye spray chromoendoscopy (Kudo classification). Buchner *et al*[25] described chromoendoscopy as a valuable tool for diagnosing colorectal abnormalities by applying a dye spray, like Indigo Carmine, to accentuate mucosal irregularities and outline the surface, border, and any depressions in polyps. Chromoendoscopy can diagnose flat or depressed lesions linked to invasive cancer, even if they are small.

Another helpful function to characterize colonic polyps is the magnification of endoscopy, which improves the visualization of pit patterns on surfaces of polyps that predict underlying pathology. Iwatate *et al*[26] reported that through magnifying chromoendoscopy, the pit patterns of the polyp could be identified, leading to risk stratification for the possibility of submucosal invasion. Type I polyps have the least risk of invasion, while type V polyps have the highest risk. This information can predict malignant changes and guide the selection of the most appropriate treatment modality.

NBI is another method that can be used to detect malignant transformation of colorectal polyps by assessment of microcapillary architecture – the meshed capillary pattern. Disorganization of this pattern indicates dysplasia. Sano classification depends on this pattern and classified polyps from I to III while III are the polyps with malignant changes. The Narrow Band Imaging International Colorectal Endoscopic (NICE) classification, also, allows examination of the surface characteristic of a polyp based on surface appearance, color, and vessel pattern. The NICE classification has a high specificity, but a low sensitivity for detecting invasive cancer, as menthioned in Hewett *et al*[27], Hayashi *et al*[28] and Zhou *et al*[29]. Sumimoto *et al*[30] described that Japanese Narrow Band Imaging Expert Team (JNET) further divides type 2 into JNET 2a (conventional adenoma) and JNET 2b (adenoma with high-grade dysplasia or superficial SMIC). The WASP criteria, based also on NBI findings, was developed to help identify sessile serrated lesions. Utsumi *et al*[31] described Flexible spectral imaging color enhancement (FICE) as an another imaging technique available with modern Fujinon colonoscopes, and detecting surface patterns can also differentiate between polyp types. FICE is quite similar to NBI, but some studies show that FICE could differentiate between neoplastic and non-neoplastic polyps without magnification.

Shibagaki *et al*[32] showed that acetic acid has been a promising addition to advanced imaging techniques for assessing colorectal polyps. When used during colonoscopy, acetic acid causes a temporary whitening of mucosal tissue, highlighting subtle changes that may indicate dysplasia or malignancy. This method facilitates the distinction between neoplastic and non-neoplastic lesions based on their reaction to acetic acid application.

Role of endoscopic ultrasound

According to Tombazzi *et al*[33], EUS holds great potential in characterizing colorectal polyps. Unlike CT and MRI, EUS provides T-stage assessment, particularly for rectal tumors. Its accuracy ranges from 55% to 91% for all stages of rectal cancer and from 25% to 98% for T1 tumors. According to a study by Hurlstone *et al*[34], demonstrated EUS's high accuracy in staging malignant polyps. Their evaluation of Paris II sessile malignant polyps accurately staged the invasion depth in 93% of cases. Furthermore, EUS plays a crucial role in assessing for residual disease after polypectomy and can identify the location of previously excised polyps, as described in Marone *et al*[35]. Despite being a method for assessing

submucosal lesions and assessing depth of invasion, EUS has certain boundaries on its application. Due to alterations in bowel wall thickness and gas interferences in right-sided colon polyps, EUS might not correctly measure deep submucosal or muscularis propria involvement. The tortuosity of the right colon and angulation can bound efficient probe placing, possibly decreasing diagnostic accurateness. Compared to high-resolution endoscopy with NBI or AI-assisted endoscopic techniques, EUS may be nominal in differentiating among fibrotic and neoplastic tissue in scarred polyps.

Histopathological examination

As explained in O'Brien *et al*[36], histological examination is critical to categorize polyps, including scarred and complex polyps, and to choose the appropriate treatment after differentiating between neoplastic and non-neoplastic polyps. Nearly 70% of colorectal polyps are of adenomatous origin and are characterized by dysplastic glandular epithelium, which might be low- or high-grade dysplasia. These adenomas can be classified into tubular, which is the most common type, with over 80% of adenomatous polyps, then tubulovillous, with nearly 15% of adenomatous polyps, and villous adenoma, with less than 5%, according to World Health Organization criteria. Also, it was found in Julka *et al*[37] that nearly 95% of cases of adenocarcinoma of the colon are of adenomatous polyp origin. Serrated lesions show distinct genetic features and structures when compared to traditional adenomas. Definite molecular pathways are closely associated with the probability of malignant transformation in serrated lesions. Recent researches have confirmed the importance of vital genetic and epigenetic adjustments, just like the strong relationship between BRAF mutations and sessile serrated lesions (SSLs) and the serrated neoplasia pathway that could give up with CpG island methylation and the development to colorectal most cancers. Typical serrated adenomas (TSAs), which have another carcinogenic path, are more likely to have KRAS mutations. The change from serrated polyps to colorectal most cancers can be augmented through high tiers of CpG island methylation that may silence tumor suppressor genes.

BRAF-mutated SSLs commonly reveal CIMP-high lesions, which are related to an increased danger of malignant conversion. Assessing theses genetic alterations may help in improving management strategies, as SSLs with BRAF mutations and CIMP-high status may need close intervals for surveillance as the risk of malignant transformation is high. KRAS-mutated TSAs might advantage from targeted therapeutic approaches.

The serrated polyps include sessile serrated adenomas, conventional serrated adenomas, hyperplastic polyps, and mixed hyperplastic/adenomatous polyps. These polyps have serration and have rapid malignant transformation when compared to others as described in Szylberg *et al*[38]. Histology of the biopsy sample from polyps is very important as it may show submucosal invasion. Qudah *et al*[39] noted that biopsy samples may not always suggest invasion into the submucosa, which can result in false-negative results when compared to the total specimen. Consequently, histopathology reports should include a requirement stating that there is no evidence of malignant transformation in the examined tissue. However, it should also alert that a more serious pathology cannot be ruled out if part of a larger lesion. So, histopathological examination of colorectal polyps is essential for making the ideal treatment decisions.

Endoscopic management strategies for scarred and complex colorectal polyps

Management of scarred and complex polyps has always been challenging, and in the early days, surgical interventions were the sole option. However, with the recent advancements in endoluminal endoscopy and resection techniques for gastrointestinal polyps and tumors, the landscape has changed significantly (Figure 1).

Gaglia *et al*[40] mentioned that argon plasma coagulation is one of the currently used modalities to treat scarred polyps, but it has a high recurrence rate. On the contrary, ESD provides *en-bloc* resection, which is highly needed, it could be technically challenging and associated with high failure rates As described in Azzolini *et al*[41]. Also, Zaghloul *et al*[14] noted that EFTR allows for *en-bloc* resection, but it is limited to polyps up to 30mm. As noted in Wilson *et al*[42], EPR is a new method recently introduced and showed promising results in the management of scarred polyp. A study in Kandiah *et al*[15] exploring the feasibility of using an EndoRotor showed a success rate of up to 84% in managing scarred polyps in the rectosigmoid colon, indicating the potential of this tool to manage scarred polyps without the need for surgery.

EMR techniques

EMR is a minimally invasive procedure used for the removal of colorectal polyps, particularly those without a stalk. Resection of the polyps by this technique is by injecting a solution into the submucosa to make a cushion which prevents deep thermal injury and reduces procedure duration. Saline is the most common agent used for injection. However, the American Society for Gastrointestinal Endoscopy recommended the use of more viscous agents such as succinylated gelatin, hydroxyethyl starch, Eleview, or glycerol as noted in Hwang *et al*[43]. These agents could help in shorter procedure duration, a lower rate of post-polypectomy bleeding, and a higher rate of successful and *en-bloc* resections. Chaptini *et al*[44] emphasized that diluted adrenaline can be used as it allows better visualization and induces vasoconstriction to reduce bleeding risk. After injection of the solution, the lesion is lifted from muscularis propria and dissected by polypectomy snare. Cold snare is also used, especially with serrated polyps sized between 10 mm and 20 mm. Mann *et al*[45] underlined that EMR can be performed either *en-bloc* or piecemeal techniques. However, *en-bloc* resection is preferred over piecemeal EMR because it allows for histological assessment of the lesion's margin, especially when malignancy or deep invasion is suspected. Additionally, the recurrence rate for individuals who undergo piecemeal EMR is 20% higher compared to *en-bloc* resection.

Underwater EMR (uEMR) is a specialized technique that enables polyps removal by filling the colon's lumen with fluid after suctioning the air. Once underwater, due to the high fat density of the polyp, it is separated from the muscularis propria, reducing the risk of snare entrapment of the muscle layer. Intraluminal water also serves as a heat sink, preventing the deeper colonic wall from thermal damage. Additionally, it is believed that uEMR reduces the risk of

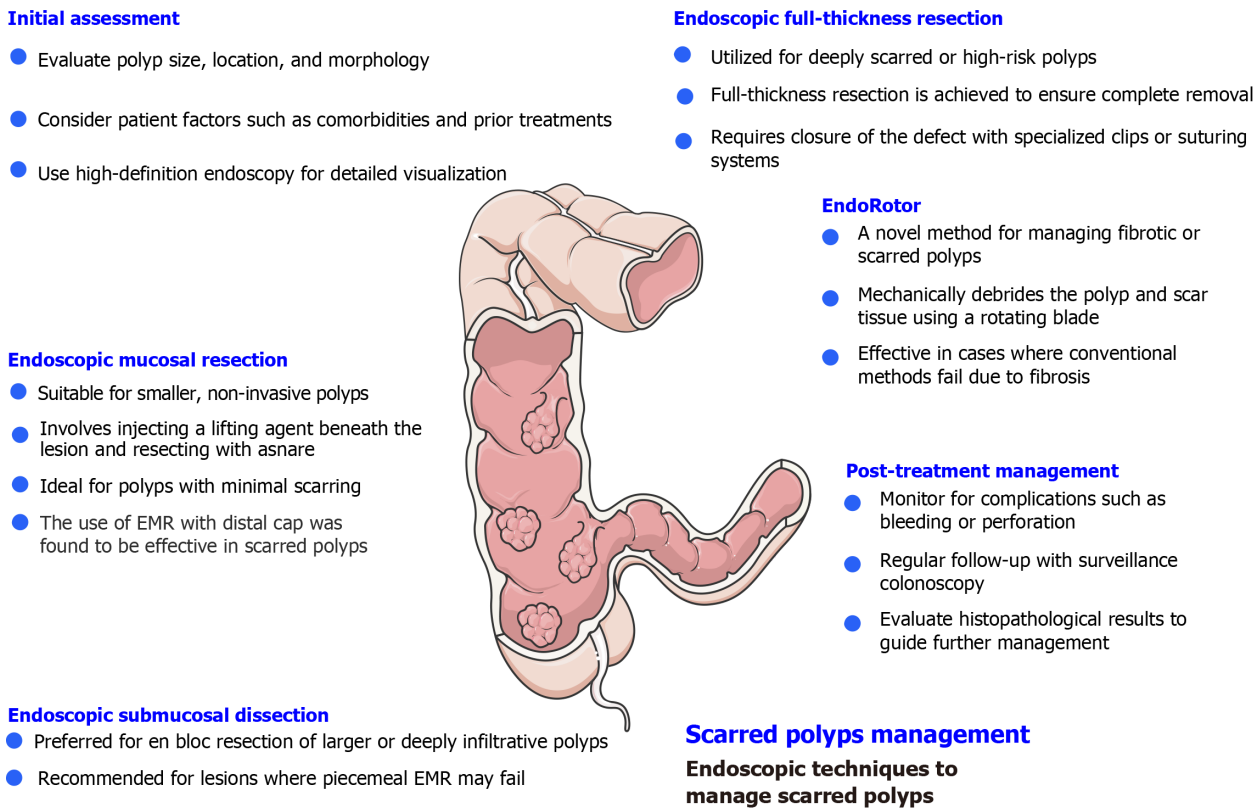


Figure 1 Summary of treatment options for scarred polyps.

recurrence, perforation, and post-polypectomy syndrome.

The primary advantage of uEMR lies in the low distension of the bowel lumen, which allows for the capture of a significantly larger mucosal surface area by the snare. Furthermore, fluid immersion reduces the colonic haustral folds, making both sides of the fold more planar, facilitating easier *en-bloc* resection, and making the management of complex polyps in terms of size achievable.

In a retrospective study in Schenck *et al*[46] comparing uEMR and standard EMR, uEMR demonstrated a higher rate of complete macroscopic resection (98.6% *vs* 87.1%) and a lower rate of recurrence (7.3% after uEMR compared to 28.3% after standard EMR), especially for large lesions > 1.5 cm. A meta-analysis prescribed in Chandan *et al*[47] that included a total of 7 trials investigating the efficacy and safety of uEMR compared to conventional EMR, reported a higher efficacy in terms of *en-bloc* resection and lower recurrence rates for uEMR.

Another EMR technique that has been reported to be effective in resecting scarred polyps is the distal cap-assisted EMR (EMR-DC) technique. In Douglas *et al*[48], a study that included 61 patients who underwent EMR-DC for scarred lesions. The authors reported a clinical success of 100% while the 6-month recurrence rate was as low as 9.8%.

ESD for large polyps

ESD, a technique that can be used to resect large polyps *en-bloc* (Figure 2), especially flat polyps, has proven to be a rescue therapy. If not for ESD, these polyps would have been piecemeal resected using EMR, making them at higher risk of recurrence. Moreira *et al*[49] described that ESD involves submucosal injection to lift the lesion, followed by a circumferential incision of the mucosa (Figure 3). After that, the submucosa above the muscularis propria is dissected. While ESD is an effective technique for managing polyps, it requires considerable technical skill and experience to be successfully and safely performed. In addition, in cases such as scarred polyps, it may not be a viable option since lifting after injection usually fails. The American Gastroenterology Association recommends ESD for large polyps to ensure complete resection or those polyps with a high risk of carcinoma involvement as noted in Draganov *et al*[50]. ESD is highly effective in managing early rectal cancers (T1, where cancer is confined to the submucosa) and offers a minimally invasive approach. Jung *et al*[51] underlined that ESD has shown promising results in the management of complex polyps, such as recurrent polyps after EMR, tumors associated with IBD, and large colorectal polyps.

EFTR

Endoscopic full-thickness resection represented a new hope for the treatment of colorectal polyps, especially complex polyps or those that have previously been manipulated. Schurr *et al*[52] noted that Over-the-scope clips have significantly enhanced the safety and practicality of EFTR. EFTR enables the resection of lesions extending deep to the submucosa, addressing challenges commonly encountered by conventional endoscopic methods or specific anatomical locations (close to a diverticulum or appendiceal orifice) as described in Mueller *et al*[53]. Zwager *et al*[54] underlined that the success rate of EFTR is approximately 83.3%, and an R0 resection rate indicates the complete removal of malignant tissue,

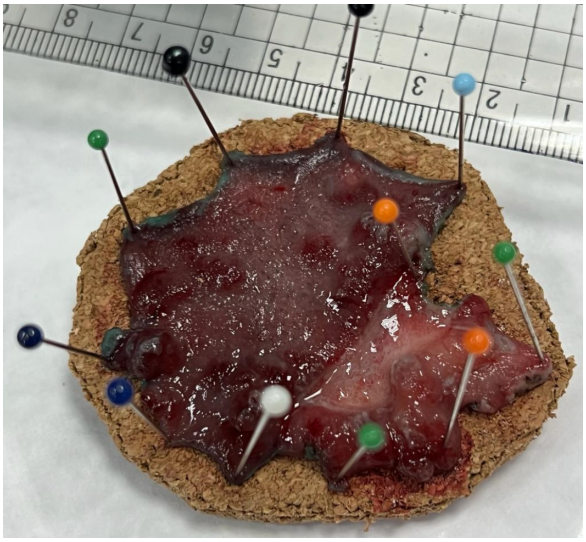


Figure 2 *En-bloc* resection by endoscopic submucosal dissection for a polyp with central scar (arrow).

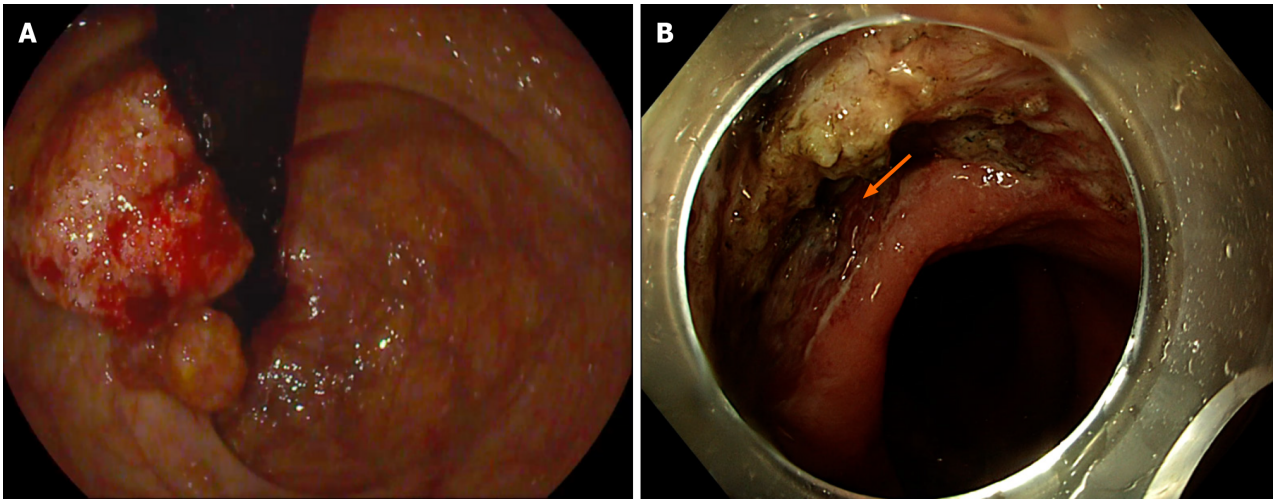


Figure 3 Endoscopic submucosal dissection. A and B: Large rectal with areas of fibrosis lesion removed by endoscopic submucosal dissection (arrow).

approaching 75%. These data underscore EFTR's ability to cure certain tumors classified as T1 or T2, particularly those smaller than 3 cm. As explained in Aslanian *et al*[55], EFTR could present a rescue therapy when conventional techniques such as EMR and ESD fail to remove the polyp due to the presence of scar tissue or worries about deeper neoplastic involvement. It has demonstrated effectiveness in removing scarred polyps that exhibit the "non-lifting sign," which complicates resections. However, careful individual assessment based on the characteristics of the lesion and the patient's health remains crucial. While EFTR provides numerous benefits, clinicians must be cautious about depth. The recommendation to use EFTR depends on the depth of fibrosis which can be assessed by endoscopic visualization as fibrotic tissue frequently looks as a inflexible, non-distensible part with decreased submucosal lifting capacity. Another method is EUS can aid define whether fibrosis is limited to the submucosa or spreads into the muscularis propria, guiding EFTR possibility. These recommendations of assessment affect the treatment strategy as in superficial fibrosis EFTR remains a viable option but in Deep Fibrosis Involving the Muscularis Propria there is high risk of perforation.

Mun *et al*[56] highlighted the potential complications associated with its use, including the risk of bleeding, perforation, appendicitis when the lesion is near the appendiceal orifice, and dehiscence due to the OVESCO clip falling off the colonic mucosa, which could lead to peritonitis and sepsis. With ongoing technological progress, the indications for procedures like EFTR are thought to expand, potentially leading to enhanced patient outcomes, not only for those with intricate polyps but also contributing to a reduction in the overall incidence of colorectal cancer.

ENDOSCOPIC POWERED RESECTION (ENDOROTOR)

The last five years have witnessed significant research on the application of EPR in the management of gastrointestinal

polyps. Zaghloul *et al*[14] reported that EPR has emerged as a promising approach that addresses some of the current challenges associated with scarred polyps. Its reported efficacy and safety in treating scarred polyps, either alone or in combination with other modalities provide an additional defense against the need for surgery for such complex polyps. In 2019, Kandiah *et al*[15], reported a cohort of 19 patients who had scarred polyps and were treated by EndoRotor. The cure rate after EndoRotor reached up to 84% of their cohort without any notable complications and with only three cases of recurrence. The first international multicenter experience of EPR was reported by Knabe *et al*[57] where the authors recruited 45 patients with a total lesion number of 48 from all over the gastrointestinal tract treated by EPR alone. The technical success was 98%, yet nearly 47% of cases had residual/recurrence after the first treatment session. The limitations of EndoRotor include the need for multiple treatment sessions, the stiffness of the device catheter, which makes it challenging to maneuver inside the lumen and impossible to retract the scope, the difficulty in using it in the upper gastrointestinal tract since it requires a working channel of 3.2 mm, which is not present in gastroscopes, and finally, the poor quality of collected samples for histopathological examination, EndoRotor usage in the upper gastrointestinal tract is limited by the rigidity of its catheter in exact anatomical positions, mainly at colonic flexures and angulated segments, like the hepatic and splenic flexures. The stiffness of the EndoRotor catheter decreases its flexibility, making navigation over sharp angulations harder. Poor catheter placing at flexures might cause partial resection, increasing recurrence rates. Excessive force applied in highly angulated regions may raise the danger of mucosal damage or perforation. To ease these challenges, other strategies can be considered, containing pre-procedural positioning changes by improving patient positioning during colonoscopy to enhance endoscopic admission. Usage of auxiliary endoscopic devices as extra accessories like stiffening overtubes or rotatable sheaths to improve device mechanism. Laparoscopic direction with endoscopic resection might be necessary, mainly for proximal colonic lesions. As highlighted in Zaghloul *et al*[14].

SURGICAL MANAGEMENT

Johnson *et al*[58] reported that the role of surgery has been significantly diminished over the past few years due to the remarkable advancements in natural orifice transluminal surgeries. Nevertheless, surgical management can still be beneficial when endoscopic techniques fail or when the characteristics of polyps exhibit complexity or deep invasive carcinoma, especially with the higher risk of colon cancer in polyps exhibiting these characteristics. Consideration of the management plan is very crucial, especially with those who have a high risk of recurrence. Laparoscopic techniques have offered management by providing less invasive compared to open surgery in terms of short recovery time, less postoperative pain, and lower incidence of complications.

Complications and outcomes of scarred and complex colorectal polyp management

Rates of incomplete resection and recurrence: The nightmare of incomplete resection rates for complex colorectal polyps poses a significant challenge in clinical practice. Various anatomical and histological factors influence the outcomes. As reported in Taghiakbari *et al*[59], research reveals that incomplete resections occur in between 2% to 27% of cases. Larger lesions, particularly those exceeding 20 mm or involving multiple colonic folds, exhibit even higher rates of residual tissue post-removal. It was also found that piecemeal resection was associated with a local recurrence rate between 10% and 20%, highlighting the importance of comprehensive pre-procedural assessments and careful selection of techniques. As noted in Tholoor *et al*[60], incomplete resections have been associated with specific polyp characteristics, which can be identified using scoring systems such as SMSA. These systems help in identifying patients at higher risk of developing residual disease and complications during endoscopic excision. An Australian multicenter retrospective study mentioned in Mangira *et al*[61], involving patients undergoing piecemeal resection of 204 polyps larger than 20 mm revealed a recurrence rate of up to 5.5% at the initial colonoscopy, and 3.5% at the second colonoscopy. Piecemeal EMR comes with higher rates of incomplete resection. Knabe *et al*[62] reported a study of 252 polyps over 20 mm found that 88.5% of polyps removed in a piecemeal fashion had a 17.1% complication rate. At 6 and 12-month follow-up colonoscopies, nearly 36% and 33% of cases showed incomplete resection and residual tissue, respectively. Additionally, a study in Desomer *et al*[63] noted that used HD white light endoscopy and NBI technique demonstrated a 26% improvement in sensitivity for detecting local recurrence.

BLEEDING

Bleeding is the most common adverse event classified to associate with endoscopic techniques used to manage scarred polyps. It is classified into two types: Intra-procedural bleeding (IPB) and post-procedural bleeding (PPB). IPB, described as any active bleeding that occurs at some point of the endoscopic procedure, necessitating direct haemostatic intervention like coagulation, clipping, or injection medication. IPB is generally known by spurting or oozing haemorrhage at point of resection. PPB is described as clinically essential bleeding that takes place after final change of the technique, classically within 24 hours to 14 days post-resection. PPB is considered with haematochezia, melena, or a drop in hemoglobin requiring clinical intervention (*e.g.*, repeat endoscopy, blood transfusion, or surgical management). Burgess *et al*[64] reported that IPB accounts for 11%–22% of cases and can be controlled endoscopically. Several factors increase the risk of intraprocedural bleeding, including the presence of large polyps, tubulovillous or villous lesions, minimally elevated sessile polyps, and limited operator experience with EMR. According to Naseer *et al*[65], to enhance visual-

ization and potentially stop bleeding from small vessels, vigorous irrigation using a water jet pump can be beneficial. Additionally, the administration of diluted adrenaline can help minimize bleeding. However, all these measures should be complemented with a second mechanical or hemostatic modality, such as coagulation forceps or endoscopic clips.

To reduce bleeding risks during EMR, Bendall *et al*[66] reported that hot-snare techniques are widely used due to their effectiveness in controlling immediate hemorrhage. However, they may lead to increased delayed bleeding. Resection of pedunculated polyps can result in severe intraprocedural bleeding that can be managed by placing a clip or a detachable snare "endoloop". Changing patients' positions can also improve visualization of the bleeding point.

PPB occurs hours to days after surgery and accounts for 2% and 11% of cases. Halme *et al*[67] described that clinically significant bleeding occurs in 6% of cases. Risk factors for delayed bleeding include lesions in the right colon, large lesions with a size greater than 40 mm, age over 75 years, antiplatelets or anticoagulants taken within seven days of the procedure, and intraprocedural bleeding. Not all patients with PPB require urgent colonoscopy. However, patients who show a response to hemodynamic resuscitation should be clinically observed first. If bleeding persists, adequate bowel preparation and a repeat colonoscopy should be performed.

PERFORATION

Perforation is another complication of endoscopic resection, particularly with advanced techniques like ESD and EFTR. A meta-analysis reported in Hassan *et al*[68], 50 studies revealed that 1.5% of patients experienced complications due to perforation post-EMR for colorectal polyps larger than 20 mm. In contrast, the perforation risk increases significantly to a range of 3.3% to 10% in patients undergoing ESD. A meta-analysis of 97 studies involving patients undergoing standard ESD showed a perforation rate of 5.2%. Notably, this meta-analysis also included 12 studies with colorectal lesions resected using hybrid ESD, resulting in a perforation rate of 4.8%. The risk of perforation further increases with complex polyps and factors such as bulky lesions exceeding 20 mm, proximal lesions, submucosal fibrosis, and inexperienced operators as explained in Fuccio *et al*[69]. Regarding EFTR, a meta-analysis reported in Dolan *et al*[70], showed a lower perforation risk of 4.4% in cases**.** Initially, this finding may seem surprising considering the invasive nature of the procedure. However, it can be explained by the fact that EFTR involves closing the lumen after resection during every procedure, either manually or using a device. Management of endoscopic perforation varies according to multiple factors such as the size, site, bowel preparation, time of detection, and general condition of the patient. For small perforations, there is no need for surgery. Tawheed *et al*[71] reported that endoscopists can manage these small perforations less than 1 cm using through-the-scope clips, while lesions in the left colon and up to 3 cm could be closed using over-the-scope clips. For larger perforations requiring more extensive closure, advanced suturing devices are necessary. Recently, endoscopic endovacuum therapy has been reported to be beneficial in certain situations where perforation occurs. The concept behind this technique is to maintain negative pressure and suction in the presence of antibacterial tap, thereby promoting healing by preventing bacterial infection, reducing edema, and enhancing blood flow as described in Tawheed *et al*[71].

POST-POLYPECTOMY COAGULATION SYNDROME

Post-polypectomy coagulation syndrome (PPCS) is a rare complication that occurs after polypectomy procedures, especially when electrosurgical current is used. However, with the recent advancements in endoscopic management of colorectal polyps, the incidence of PPCS may be on the rise. Arimoto *et al*[72] noted that the risk of developing PPCS ranges from 0.03% to 1.2% of polypectomy procedures. PPCS typically presents with similar symptoms to bowel perforation, such as fever, abdominal pain, and signs of peritonitis. However, it has a better prognosis. Early diagnosis is crucial to prevent unnecessary surgery, as PPCS usually responds well to medical treatment. Several factors increase the risk of developing PPCS, including the presence of complex polyps (in terms of size, location, and scarring), and a history of hypertension as explained in Arimoto *et al*[72] and Ito *et al*[73].

ESGE GUIDELINES 2024

The ESGE 2024 guidelines offer critical updates on the control of complicated and scarred polyps (Figure 4), emphasizing threat stratification and proof-based medication selection. Key suggestions include risk-based Approach to Polypectomy as ESGE now advocates for a dependent type machine to determine whether EMR, ESD, or EFTR is the suitable technique for a given lesion. Expanded Role of AI and Molecular Markers by highlighting the combination of AI-assisted endoscopic evaluation and molecular in predicting malignant transformation threat. Eventually technical Refinements in ESD and EFTR, ESGE 2024 introduces refinements in ESD approach, in particular in handling fibrotic lesions, and reinforces EFTR as a favored option for deeply scarred or non-lifting polyps with fibrosis Grade II. A useful tool for comparing deep mucosal invasion and directing endoscopic choice-making is the Sydney DMI categorising system. Classification of Sydney DMI Lesions, which can be restricted to the mucosal layer and suitable for EMR, are known as DMI-1. DMI-2, shallow submucosal invasion, and in certain situations, ESD may be used for resection. DMI-3, massive submucosal invasion, often necessitating surgical procedure or EFTR.

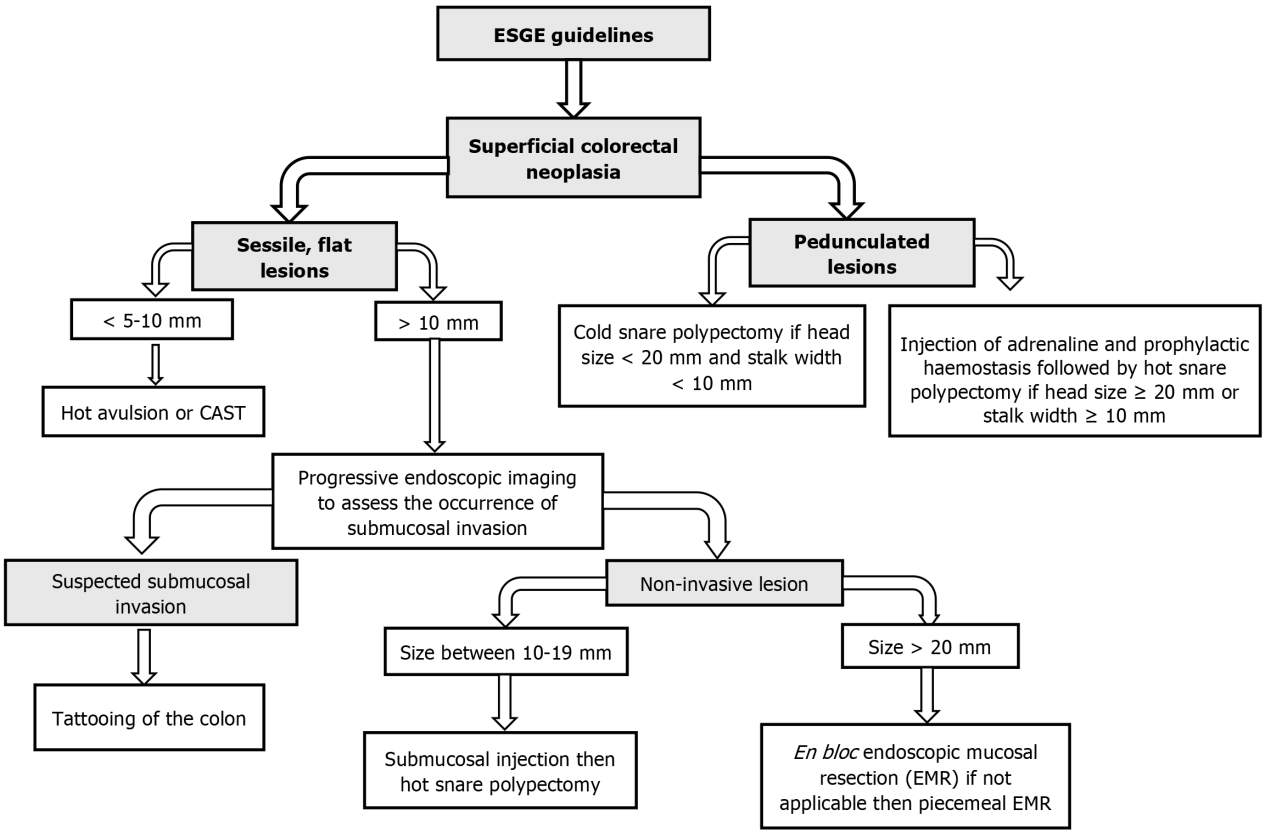


Figure 4 Summary of the ESGE 2024 guidelines.

CONCLUSION

Scarred polyps of the colon and rectum pose a significant challenge in clinical practice. Due to their high association with recurrence and increased risk of developing adenocarcinoma, successful resection is essential. However, there is no clear definition for the term "scarred" or "complex" polyps, and various scoring systems have been introduced to stratify the difficulty of polyp resection. Additionally, there is a lack of consensus or guidelines providing endoscopists with a clear framework for managing these polyps. Currently, EMR, ESD, EFTR, and EPR are used to treat these polyps, but none of these modalities have been extensively studied to determine their effectiveness in managing the challenging morphology of these polyps. Therefore, research should focus on refining the criteria for utilizing the currently used techniques to manage scarred polyps. Establishing a systematic framework is essential to assess the effectiveness of these advanced methodologies compared to traditional approaches. Also, a multidisciplinary approach is crucial throughout the entire process, from initial diagnosis to treatment planning and post-procedural follow-up care. Collaboration among gastroenterologists, surgeons, pathologists, and oncologists is essential to ensure the effectiveness of the management plan, which is tailored to each patient's condition and lesion characteristics. Even while endoscopic resection strategies have advanced, current research is regularly confined as several research assessing EFTR, ESD, and other modern techniques are done at high-extent centres with professional operators, which introduces the first bias. This restricts generalisability because real-global results might vary in contexts with lower volume. The second element is operator dependency; methods like hybrid ESD and EFTR necessitate an excessive stage of technical talent and have an effect on reproducibility in numerous medical contexts. Because of their choice bias, studies generally omit situations which are technically hard, which ends up in published findings which can be unduly positive. The long-term efficacy of extra current modalities, especially AI-assisted diagnostic method, is in the long run understudied due to a loss of longitudinal statistics. Multicenter trials and standardised training procedures should be given top priority in future with a view to increase statistics dependability and expand the use of modern technology.

FOOTNOTES

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MINIREVIEWS

Role of irisin in physical activity, sarcopenia-associated type 2 diabetes, and cardiovascular complications

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Abstract

Irisin is a chief myokine released during physical activity and has garnered attention for its potential therapeutic effects on different metabolic and cardiovascular disorders. This review explores the intricate connections between irisin, physical activity, sarcopenia, type 2 diabetes mellitus (T2DM), and cardiovascular complications. Experimental data suggests that through irisin release, physical activity positively influences muscle health, metabolic regulation, and cardiovascular function. In individuals with sarcopenia, characterized by progressive muscle mass and function loss, irisin plays a pivotal role in maintaining muscle integrity and function. Additionally, irisin's beneficial effects on insulin sensitivity and glucose metabolism suggest its involvement in the pathophysiology of T2DM. The review will examine how irisin may modulate the development of cardiovascular complications, particularly in the context of diabetes and aging. Additionally, it will explore its potential as a therapeutic target for managing sarcopenia, T2DM, and cardiovascular complications, underscoring the importance of physical activity in mitigating these interconnected health challenges. Further research is needed to elucidate the precise mechanisms by which irisin mediates these effects and assess its clinical applicability in preventing and treating metabolic and cardiovascular disorders.

Key Words: Type 2 diabetes mellitus; Exercise; Myokines; Irisin; Sarcopenia; Vascular complications

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Core Tip: Physical inactivity, sarcopenia, and diabetes are interrelated conditions, each exacerbating the others. The impact of these issues is significant, particularly on the cardiovascular system. Irisin, a myokine with autocrine, paracrine, and endocrine functions, may play a key role in metabolic health and could serve as an adjunct to the pharmacological management of prediabetes and diabetes. The exact mechanisms through which irisin exerts its beneficial effects, and the optimal levels for the therapeutic potential, need further investigation. Moreover, assessing irisin levels in response to different exercise types and intensities could be valuable in customizing individualized exercise plans for patients with diabetes and related complications.

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INTRODUCTION

Diabetes mellitus is a widespread metabolic disease with a rising incidence that parallels the advancement of age. Although its pathophysiology is complex, type 2 diabetes mellitus (T2DM) and its early-stage precursor, prediabetes, are largely driven by unhealthy lifestyles, including low levels of physical activity and sedentary behavior, which are closely interrelated with insulin resistance (IR), a hallmark of T2DM[1]. Despite extensive research and efforts dedicated to developing individually tailored pharmacotherapy, the management strategies of T2DM remain challenging and often fail to achieve the desired effects, leading to chronic complications that drive unfavorable outcomes[2]. In this vicious cycle, one of the important players is sarcopenia, an age-related condition characterized by a reduction in muscle mass, strength, and function accentuated by physical inactivity and closely linked to physical disability, compromised glycemic control, poor quality of life, and finally, mortality[3]. Unfortunately, sarcopenia is often overlooked, especially in persons with high body mass index, which is often in T2DM. Currently, several diagnostic methods are available for this purpose, ranging from non-invasive, easily accessible, and harmless bio-electrical impedance analysis to less commonly used methods that may involve higher costs, limited accessibility, and potential risks. These include dual-energy X-ray absorptiometry, magnetic resonance imaging, and computed tomography, the latter of which is considered the gold standard for quantifying muscle mass[4].

In patients with T2DM, the incidence of sarcopenia is 2-3 times higher compared to patients without T2DM, and sarcopenia and insufficient physical activity are both independently correlated with the onset of T2DM. On the other hand, a 10% increase in skeletal muscle index decreases the HOMA-IR by 11% and the incidence of prediabetes by 12% [5]. Sarcopenia is extensively found in older adults with T2DM, where it correlates with high HbA1c and macrovascular and microvascular complications of diabetes[6]. Several studies have demonstrated an association between sarcopenia and an increased risk of atherosclerosis, the prevalence of coronary calcification, and major adverse cardiovascular events. Additionally, the presence of microvascular diabetic complications, such as retinopathy, nephropathy, and neuropathy, heightens the risk of developing sarcopenia. The mechanisms linking these factors include IR, chronic inflammation, and advanced glycation end-products, which are exacerbated by reduced mobility, a feature common among patients with comorbid T2DM[7].

PHYSICAL (IN) ACTIVITY, SARCOPENIA, AND DIABETES

Numerous studies and lifestyle intervention programs have shown that engaging in physical activity can provide significant metabolic benefits, often comparable to pharmacological treatments for individuals with prediabetes and early-stage diabetes[8]. Recent molecular research has highlighted that muscle contraction can serve as an underutilized therapy for individuals with metabolic disorders independently or in conjunction with other treatments[9,10]. Indeed, evidence from original studies with decades-long follow-ups, such as Da Quing and the Diabetes Prevention Program, supports lifestyle interventions, including physical activity, in diabetes reversal and prevention[11,12]. This therapeutic effect is mediated through the skeletal muscle either directly, by diminishing peripheral IR and increasing muscular glucose uptake, or indirectly, *via* its endocrine function, supported by the release of over 600 myokines like myostatin, interleukin-6, interleukin-15, myonectin, *etc*., with irisin potentially playing a central role in metabolic regulation[13-16].

IRISIN- A LINK LIGHTING FIRE BETWEEN MUSCLE AND METABOLIC HEALTH?

Skeletal muscle is crucial for movement and physical strength and functions as a vital endocrine organ. Recent research has uncovered its role in regulating metabolism and preventing metabolic diseases such as diabetes. When muscles contract, they release various signaling molecules known as myokines. One of the most significant ones for metabolic health is irisin, primarily (more than 72%) secreted by skeletal muscle, and in smaller amounts by heart, adipose tissue,

and liver[17]. It is derived from a larger precursor, fibronectin type III domain-containing protein 5, a membrane-spanning protein cleaved to form irisin by an unknown protease[18]. Irisin synthesis and secretion are induced by acute bouts of exercise and peroxisome proliferator-activated receptor-γ coactivator 1-α, but irisin expression appears to be influenced by age, gender, and obesity[19]. Once secreted, irisin can regulate glucose homeostasis in skeletal muscle in an autocrine manner by stimulating glucose uptake *via* p38 mitogen-activated protein kinase-glucose transporter 4 translocation[20]. In addition, irisin can improve the expression of uncoupling protein 1 and promote the browning of white adipose tissue, increasing mitochondrial density, and potential for aerobic glycolysis with greater energy expenditure[21].

Furthermore, irisin could protect muscles from deterioration and dysfunction, and thus prevent diabetic myopathy. A potential explanation is the reduction of hyperglycemia and inflammation, and consequently diminished IR, and improved insulin sensitivity[22]. In rodent models, irisin's myogenic role was shown through the induction of skeletal muscle hypertrophy and at the same time attenuation of atrophy by activating interleukin (IL)-6, satellite cells, and protein synthesis[23]. Moreover, a study by Park *et al*[24] showed that irisin may function as a potential promyogenic factor in postmenopausal sarcopenia. Irisin also acts on the adipose tissue, stimulating white adipocyte browning and thermogenesis and reducing visceral fat[25,26]. Moreover, experimental studies showed that irisin has anti-apoptotic actions on pancreatic beta-cells which can stimulate their proliferation, insulin biosynthesis, and secretion[27,28]. Although measurement of irisin concentration is still challenging and faces many discrepancies related to the methodology used (for example tandem mass spectrometry *vs* ELISA)[29], human studies have consistently shown lower irisin levels in sera of diabetic patients compared to healthy controls[20,30-32].

Besides, studies have shown a link between low circulating irisin levels and muscle weakness and atrophy, suggesting its potential as a biomarker of sarcopenia[33,34], and sarcopenic obesity, a common finding in T2DM patients[35]. A study by Oguz *et al*[36] showed irisin levels were significantly lower in patients with T2DM with sarcopenia (10.07 ± 6.17 ng/mL) compared to those measured in patients with T2DM and no sarcopenia (13.67 ± 9.07 ng/mL), $P = 0.038$. In contrast, the lowest irisin levels were detected in patients with T2DM and sarcopenic obesity (7.66 ± 5.27 ng/mL), so the authors suggested an irisin value of < 9.49 ng/mL to be a cut-off for detecting sarcopenic obesity with sensitivity and specificity of 75.8% and 78.1%, respectively[36]. When serum irisin levels were compared between T2DM patients with and without vascular complications, prior had the lowest values, suggesting irisin could be used as a biomarker to further stratify diabetic patients according to their potential risk of developing micro and macrovascular complications[36-39].

CAN IRISIN SLOW DOWN/REVERT THE DIABETIC VASCULAR COMPLICATIONS?

In people with T2DM, sarcopenia increases the risk of developing cardiovascular complications [cardiovascular disease (CVD), hazard ratio (HR) = 1.89, heart failure (HR = 2.59), stroke (HR = 1.90), and myocardial infarction (HR = 1.56)], which might occur 14.5 years earlier than in those without sarcopenia[40]. The risk factor connecting T2DM and CVD is muscle strength, which is lower in the diabetic population, where the prevalence of sarcopenia ranges between 7% and 29.3% and is potentially associated with excess CVD risk[41,42]. The molecular mechanisms responsible for complications are still not fully understood. However, it seems that chronic inflammation and oxidative stress play significant roles in their development through the promotion of atherosclerosis[43]. Studies suggest that irisin can reduce markers of inflammation, such as tumor necrosis factor-alpha and IL-6, which are elevated in diabetes and contribute to CVD. Moreover, irisin could protect the heart by improving endothelial function and exerting anti-inflammatory and antioxidant properties[44]. In a study comparing 350 patients with coronary artery disease with 214 healthy participants, low irisin levels were characteristic of the prior, and inversely correlated with the severity of atherosclerosis expressed using a coronary atherosclerosis index[45]. A similar correlation was also found for carotid artery intima-media thickness. Both findings are mainly speculated to be driven by irisin's regulation of glucose and lipid metabolism, while another explanation lies in the cross-talk between irisin and molecules such as sclerostin and adipocytokines, involved in atherosclerosis[46,47]. Explanations for the direct irisin's effect on the prevention of atherosclerosis originate mainly from animal studies and are still controversial. They include the regulation of endothelial function, through suppression of inflammation and oxidation, activation of eNOS signaling, reduction of oxidative stress, inhibition of the generation of reactive oxygen species, and the nuclear translocation of NF-kB. In addition, irisin might also act on macrophages, slowing down plaque formation[19].

Although research is still in the early stages, there is evidence that irisin might prevent or reduce the severity of diabetic microvascular complications- nephropathy and retinopathy by promoting cellular repair and reducing inflammation[44,48]. Preliminary studies show irisin might also exert neuroprotective mechanisms, and promote nerve regeneration[48]. The production of irisin is largely triggered by muscle contraction during exercise. Regular physical activity that strengthens the muscles is expected to improve their function as an endocrine organ. Consequently, muscle-derived irisin could serve as a promising therapeutic target. However until the evidence is gathered from the large-scale prospective cohort studies validating the causal relationship between irisin levels and diabetic complications, irisin's true potential to prevent or treat vascular complications is speculative. Understanding the effects of different types of exercise on an individual level is crucial for optimizing and enhancing metabolic health.

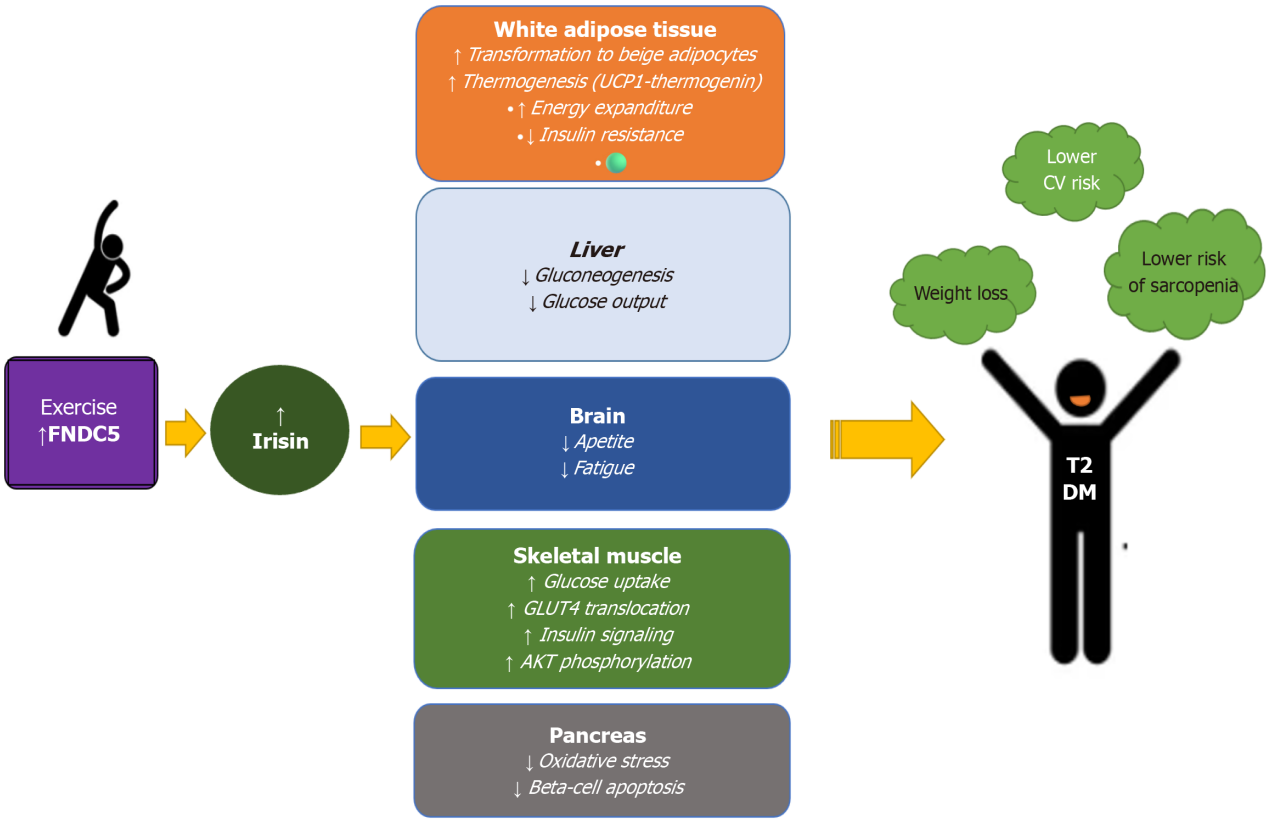


Figure 1 Exercise as a promotor of irisin, a potential key mediator of the beneficial effects of exercise on glucose metabolism, insulin sensitivity, and energy metabolism. CV: Cardiovascular; T2DM: Type 2 diabetes mellitus.

IRISIN LEVELS IN AEROBIC, RESISTANCE, AND HIGH-INTENSITY TRAINING: IS IT TIME TO OPTIMIZE AND INDIVIDUALIZE EXERCISE TREATMENT FOR DIABETIC PATIENTS?

Studies exploring the effects of physical exercise on irisin levels have yielded varying results suggesting exercise type, intensity, and duration, besides an individual's age, sex, and fitness level, might be important factors influencing irisin levels[49]. Aerobic exercise increases *FNDC5* expression, which leads to the irisin release. Long-term moderate-intensity aerobic training increases irisin levels, which might be an explanation for the way it influences body composition and insulin sensitivity[50]. In addition, endurance training leads to a significant increase in irisin serum levels in middle-aged/older individuals, which inversely correlates with the reduction of visceral fat[51].

Resistance training and skeletal muscle contraction can activate PGC-1α and consequently increase irisin production [52,53]. Evidence suggests that a single bout of resistance exercise causes significantly greater elevations in plasma irisin compared to those after endurance exercise alone or after the same duration of combined resistance and endurance exercises[53]. A recent meta-analysis involving only data available from randomized control trials with a control group and including 921 participants (64% in the intervention group) suggests that physical exercise significantly increases circulating irisin and at the same time decreases insulin, glucose, and IR. For patients with prediabetes and T2DM, the best results can be achieved with resistance and combined training[54]. Although there is limited research on the effects of high-intensity training on irisin production and release, it seems it may increase irisin levels in T2DM patients, regardless of the interval or continuous modality of training[55]. Utilizing findings on physiological irisin levels in the human population is crucial for assessing exercise-based therapies, considering variations in ethnicity, age, weight, sex, and metabolic status. A key challenge is separating the metabolic benefits of exercise-induced irisin from the energy expenditure it brings. Achieving therapeutic irisin levels may require more than exercise alone. Current alternatives include antidiabetic agents like metformin and GLP-1RA, which boost *FNDC5* expression, and inorganic nitrate, as shown in studies with beetroot juice[56,57]. Future research should clarify how irisin is released and cleared during different types of exercise. This, together with better defining basal irisin levels, is a prerequisite for its potential therapeutic use[58-60] (Figure 1).

CONCLUSION

Irisin is emerging as a promising molecule in the context of sarcopenia and diabetes. Experimental evidence of effects on insulin sensitivity, fat browning, inflammation, and diabetic complications suggest that it could offer a novel approach to managing and mitigating the long-term effects of diabetes, Despite promising results from animal models, clinical studies

in humans are still limited and give conflictive results. The exact mechanisms through which irisin exerts its beneficial effects and the optimal levels for the therapeutic potential need further investigation. Moreover, future research is required to determine whether strategies to increase irisin levels—such as physical exercise, pharmacological agents, or supplementation—could serve as an effective adjunct to conventional diabetes treatment.

FOOTNOTES

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MINIREVIEWS

Uncovering the role of microbiota and fecal microbiota transplantation in Crohn's disease: Current advances and future hurdles

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Abstract

Crohn's disease (CD) is an idiopathic, chronic, and recurrent inflammatory condition of the gastrointestinal tract. Recent studies suggest a potential role of gut microbiota in CD, particularly dysbiosis—an imbalance in gut bacteria. While dysbiosis is consistently observed in CD, it remains uncertain whether it is a cause or a consequence of the disease. Given its association with CD, the therapeutic potential of fecal microbiota transplantation (FMT) has been explored. This review examines the role of gut microbiota in CD, evaluates the therapeutic potential of probiotics and FMT, and highlights current research findings and limitations. Key studies on the relationship between gut dysbiosis, probiotics, and FMT in CD were analyzed, with a focus on randomized trials, meta-analyses, and clinical observations. Dysbiosis is a consistent feature of CD, but its causative role remains unclear. Probiotics, prebiotics, and synbiotics have shown no efficacy in inducing or maintaining remission in CD. FMT shows potential as a therapeutic option for CD, but its efficacy remains inconsistent and inconclusive. The variability in outcomes, including diminished effects over time despite repeated FMT, underscores the need for larger, well-controlled trials. Only one randomized controlled trial (RCT) has compared FMT with sham transplantation, but the sample size was very small. Other studies are limited by factors such as small sample sizes, lack of control groups, short follow-up periods, and inconsistent methodologies, making it challenging to draw definitive conclusions. While gut dysbiosis likely plays a role in CD pathogenesis, its causative role remains uncertain. Current evidence does not support FMT as a reliable treatment for inducing or maintaining remission in CD, though it appears generally safe. Larger, standardized, RCTs are necessary to clarify the therapeutic role of FMT in CD management.

Key Words: Microbiota; Microbiome; Dysbiosis; Fecal microbiota transplantation; Crohn's disease

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Core Tip: This article reviews the role of microbiota in Crohn's disease (CD) and the effects of fecal microbiota transplantation. CD is a chronic, relapsing condition with a complex pathogenesis involving genetic and environmental factors. The gut microbiota, crucial for various bodily functions, shows dysbiosis in CD, with a reduction in beneficial microbes. This review highlights recent developments in understanding microbiota's role in CD and its potential in treatment strategies.

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INTRODUCTION

Crohn's disease (CD) is an idiopathic, chronic, and recurring inflammatory condition affecting the gastrointestinal tract[1,2]. More than a million people worldwide are affected by CD, with its incidence climbing for reasons that are not yet fully understood. The disease tends to be more common in those over 45 years old, with no significant difference observed between genders[2].

PATHOGENESIS

The pathogenesis of CD is a multifaceted process that includes the interaction between genetic predisposition and environmental triggers, culminating in a dysregulated immune response and intestinal inflammation[3].

The study of the microbiota's role in CD is an evolving field with numerous recent developments and ongoing challenges. Dysbiosis, defined as an imbalance in gut bacteria, has been observed in CD; however, it is difficult to determine whether it is the cause or consequence of CD.

MICROBIOTA

Microbiota refers to the microorganisms in a particular environment, while the microbiome encompasses all the genetic content of those microorganisms[4]. The human gut harbors approximately 100 trillion microorganisms, representing over 1000 different species[4,5]. While bacteria constitute the majority, other microorganisms such as viruses, fungi, and protozoa are also part of the human gut microbiota[4]. The colon contains the highest concentration of microorganisms in the human body, with an estimated 3.9×10^{13} microbes[5]. The gut microbiota plays a specific role in the host's nutrient and drug metabolism, maintaining the structural integrity of the gut's mucosal barrier, modulating immune function, and defending against pathogens[6].

ROLE OF MICROBIOTA IN THE PATHOGENESIS OF CD

The study of the microbiota's role in CD is an evolving field. Dysbiosis, defined as an imbalance in gut bacteria, characterized by a reduction in beneficial microbes and an increase in potentially harmful ones. There is difficulty in distinguishing cause and effect—whether dysbiosis is a cause or a consequence of CD[5]. Patients with inflammatory bowel disease (IBD) show a decreased presence of beneficial microbes, including Clostridioides, Bacteroides, Sutterella, Roseburia, Bifidobacterium, and Faecalibacterium. Concurrently, there is an increase in harmful bacteria, including Escherichia, Salmonella, Yersinia, Desulfovibrio, Helicobacter, and Vibrio[7-9].

EFFECT ON IMMUNITY

Microbial dysbiosis seen in CD causes alterations in host immunity, leading to aberrant activation of T-helper cells and a decrease in regulatory T cells. This imbalance results in an increase in pro-inflammatory cytokines such as interleukin

(IL)-6, IL-23, and tumor necrosis factor-α, which, in turn, exacerbate inflammatory response in CD patients[10-12].

ALTERATION IN MICROBIAL METABOLITES

Short-chain fatty acids (SCFAs), which are produced by intestinal microbes, are often reduced in dysbiosis due to a decline in SCFA-producing bacteria. When SCFA levels are low, their anti-inflammatory effects are diminished, which can lead to increased inflammation[13].

INTERACTION WITH HOST GENETICS

NOD2 gene mutations, commonly observed in CD patients, impair bacterial sensing and clearance. This genetic susceptibility, along with an increase in potentially harmful bacteria seen in microbial dysbiosis, contributes to an aggravated inflammatory response in CD[12].

DYSBIOSIS AND EPITHELIAL BARRIER FUNCTION

Microbial dysbiosis, by triggering an aggravated inflammatory response, leads to increased intestinal permeability due to the disruption of the epithelial barrier. This increases susceptibility to harmful or pro-inflammatory bacteria, further exacerbating the inflammatory response in CD[14].

The gut microbiota seems to play an important role in the pathogenesis of CD. Dysbiosis could lead to inappropriate interactions with the intestinal innate immunity, causing a cascade of host-microbe reactions that trigger an inflammatory response in genetically susceptible patients.

Ma *et al*[13] studied the role of dysbiosis in gut microbiota in early CD and its impact on the progression of the disease. The study included 18 early CD patients, 22 advanced CD, and 30 healthy control individuals. The study found elevated levels of *Lachnospiraceae incertae sedis* and *Parabacteroides* in early CD, whereas *Escherichia/Shigella*, *Enterococcus*, and *Proteus* were more prevalent in advanced cases. In contrast, healthy individuals exhibited higher levels of *Roseburia*, *Gemmiger*, *Coprococcus*, *Ruminococcus*, *Butyricicoccus*, *Dorea*, *Fusicatenibacter*, *Anaerostipes*, and *Clostridioides*. The study also revealed that microorganisms such as *Blautia*, *Clostridioides*, *Coprococcus*, *Dorea*, and *Fusicatenibacter* progressively declined with the progression of CD, while *Escherichia/Shigella* and *Proteus* levels steadily increased. The study highlighted that the steady decline in SCFA-producing bacteria as CD progresses significantly disrupts the integrity of the intestinal epithelium and promotes inflammation. Furthermore, the increase in harmful microbes exacerbates gut dysbiosis, thereby contributing to disease progression.

Zhou and Zhi's meta-analysis, which included 9 studies involving 706 patients, examined the relationship between Bacteroides levels and CD[9]. The analysis found that Bacteroides levels were significantly lower in patients with active CD compared to healthy controls. Although Bacteroides levels were also reduced in patients with CD who were in remission compared to controls, the levels remained lower in those with active disease[9].

Gevers *et al*[15] investigated the relationship between microbiota and CD in children aged 3 to 17 years, including 447 patients with CD and 221 healthy controls. The study found that, overall, microbiome diversity did not differ significantly between CD patients and healthy controls. However, specific microbes were positively correlated with CD activity. Notably, *Enterobacteriaceae*, *Bacteroidales*, *Clostridioides*, Pasteurellaceae (including *Haemophilus spp.*), *Veillonellaceae*, *Neisseriaceae*, and *Fusobacteriaceae* showed a positive correlation with disease severity. Additionally, the study found that CD negatively correlated with certain microbes, such as Bacteroides, *Faecalibacterium*, *Roseburia*, *Blautia*, *Ruminococcus*, *Coprococcus*, and the families *Ruminococcaceae* and *Lachnospiraceae*. The study also compared the microbiomes of CD patients with and without antibiotic exposure and found that antibiotics aggravated microbial dysbiosis.

Prosberg *et al*[16] conducted a meta-analysis that included 3 prospective and 7 cross-sectional studies to examine the association between microbiota and IBD activity. 5 studies included 231 patients with CD. The authors found that IBD patients exhibit a distinct gut microbiota profile compared to healthy individuals, characterized by reduced diversity and alterations in specific bacterial taxa. Notably, their findings revealed that patients with CD had reduced levels of *Clostridioides*, *Faecalibacterium prausnitzii*, and *Bifidobacterium*. These microbial shifts were associated with disease activity, suggesting that gut microbiota composition may influence CD pathogenesis and could serve as a potential biomarker for disease activity.

The findings of the above-mentioned studies are summarized in Table 1.

ROLE OF PROBIOTICS

Since intestinal microbial dysbiosis is thought to play a role in the development of CD, the roles of probiotics, prebiotics and postbiotics in the treatment of CD have been investigated. Probiotics are live microorganisms that provide health benefits, prebiotics are nutrients that nourish these beneficial microbes, and postbiotics are health-promoting substances produced by probiotics[17]. In a review by Ma *et al*[18], which analyzed 53 clinical trials on probiotics/prebiotics, and

Table 1 Gut microbiota in Crohn's disease

Ref.	Participants	Key findings
Ma *et al* [13]	Prospective cohort study (18 early CD, 22 advanced CD, 30 healthy control)	Elevated levels of Lachnospiraceae incertae sedis and Parabacteroides in early CD. Escherichia/Shigella, Enterococcus, and Proteus were more prevalent in advanced cases. Higher levels of Roseburia, Gemmiger, Coprococcus, Ruminococcus, Butyricicoccus, Dorea, Fusicatenibacter, Anaerostipes, and Clostridioides. Steady decline in short chain fatty acid-producing bacteria as CD progresses
Zhou *et al* [9]	Meta-analysis (9 studies with 706 patients)	Bacteroides levels were significantly lower in patients with active CD compared to healthy controls. Reduced levels of Bacteroides were associated with CD activity
Gevers *et al*[15]	Observational case-control study (447 patients with CD, 221 healthy control)	Enterobacteriaceae, Bacteroidales, Clostridioides, Pasteurellaceae (including Haemophilus spp.), Veillonellaceae, Neisseriaceae, and Fusobacteriaceae showed a positive correlation with CD severity. Bacteroides, Faecalibacterium, Roseburia, Blautia, Ruminococcus, Coprococcus, and the families Ruminococcaceae and Lachnospiraceae negatively correlated with CD. Dysbiosis observed in CD patients. Antibiotics aggravated microbial dysbiosis
Prosberg *et al*[16]	Meta-analysis. Total 10 studies including CD and ulcerative colitis. 5 studies with 231 CD patients.	Reduced levels of Clostridioides, Faecalibacterium prausnitzii, and Bifidobacterium in CD patients. Dysbiosis may be involved in the activity of IBD

CD: Crohn's disease; IBD: Inflammatory bowel disease.

synbiotics (mixture of probiotics) in IBD, 5 studies focused on inducing remission in active CD, with mixed results and only mild benefits observed. Ten additional studies assessed the role of probiotics in maintaining remission, most of which found them ineffective. The review concluded that current evidence did not support the use of probiotics for either induction or maintenance of remission in CD[18].

ROLE OF PROBIOTICS IN INDUCING REMISSION IN CD

Gupta *et al*[19] reported that 4 children with mild to moderate CD showed significant improvement in clinical activity with the use of probiotics. However, their study lacked a control group and had a very small sample size.

Schultz *et al*'s double-blinded randomized controlled trial (RCT) included 5 CD patients who received probiotics and 6 CD patients in the control group. They reported no beneficial effects of probiotics[20].

Fujimori *et al*[21] reported a decrease in CD Activity Index (CDAI) with the use of probiotics in 10 CD patients. However, their study did not include a control group.

Steed *et al*'s double-blinded RCT included 13 patients in the probiotics treatment group and 11 in the control group[22]. They reported a significant decrease in CDAI with the use of probiotics.

The findings of the above-mentioned studies are summarized in Table 2.

The studies showed some benefits of probiotics in CD; however, the lack of control groups and the small sample sizes in most studies are significant limitations. Therefore, more placebo-controlled trials are needed before probiotics can be recommended for inducing remission in CD.

PROBIOTICS IN THE MAINTENANCE OF REMISSION IN CD

Garcia *et al*'s RCT included 14 CD patients who received probiotics and 17 CD patients in the control group[23]. They reported improved intestinal permeability in CD patients in remission with the use of probiotics.

Bourreille *et al*'s double-blinded RCT, which included 80 CD patients in the treatment group and 79 in the control group, did not find any beneficial effects of probiotics[24].

Bjarnason *et al*'s RCT also did not show any beneficial effects of probiotics[25]. Their study included 33 CD patients in the treatment group and 29 in the control group.

Marteau *et al*'s double-blinded RCT, which included 48 CD patients in the treatment group and 50 in the control group, did not find any beneficial effects of probiotics[26].

The findings of the above-mentioned studies are summarized in Table 3.

The results of these clinical trials on probiotics for CD have demonstrated either ineffectiveness or inconsistent outcomes.

ROLE OF FECAL MICROBIOTA TRANSPLANTATION

Wu *et al*'s study demonstrated the positive effects of fecal microbiota transplantation (FMT) in animal models[27]. They explored the effects of FMT in a mouse model of CD induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS). Fecal microbiota was collected from both CD patients and healthy controls and then transplanted into TNBS-induced CD mice.

Table 2 Role of probiotics in inducing remission in Crohn's disease

Ref.	Type of study	Number (*n*)	Findings
Gupta *et al*[19]	Open label	4 CD patients. No control group	Improvement in clinical activity
Schultz *et al*[20]	DB RCT	Treatment group (*n* = 5). Control group (*n* = 6)	No benefits of probiotics
Fujimori *et al*[21]	Open label	10 CD patients. No control group	Decrease in CDAI
Steed *et al*[22]	DB RCT	Treatment group (*n* = 13). Control group (*n* = 11)	Decrease in CDAI

CD: Crohn's disease; DB: Double blind; RCT: Randomized controlled trial; CDAI: Crohn's disease activity index.

Table 3 Role of probiotics in the maintenance of remission in Crohn's disease

Ref.	Type of study	Number (*n*)	Findings
Garcia *et al*[23]	RCT	Treatment group (*n* = 14). Control group (*n* = 17)	Improvement in clinical activity
Bourreille *et al*[24]	DB-RCT	Treatment group (*n* = 80). Control group (*n* = 79)	No benefits of probiotics
Bjarnason *et al*[25]	RCT	Treatment group (*n* = 33). Control group (*n* = 29)	No benefits of probiotics
Marteau *et al*[26]	DB RCT	Treatment group (*n* = 48). Control group (*n* = 50)	No benefits of probiotics

DB: Double blind; RCT: Randomized controlled trial.

The study found that FMT from healthy donors improved CD symptoms, whereas FMT from CD patients exacerbated them. FMT also influenced inflammatory cytokines, such as IL-6, IL-1β, tumor necrosis factor-α, interferon-γ, macrophage chemotactic protein-1, leptin, and adiponectin, in the serum, colon, and mesenteric adipose tissue. These levels worsened with FMT from CD patients but improved with FMT from healthy controls[27]. While this study demonstrated the positive effects of FMT in an animal model, evidence supporting its use for treating CD in humans remains insufficient.

A 2023 Cochrane review examined 12 studies involving 550 participants to assess the role of FMT in IBD[28]. None of these studies specifically evaluated FMT for inducing remission in active CD. Only one study, by Sokol *et al*[29], which included 17 patients, explored the use of FMT for maintaining remission in CD. In this study, 17 patients were included: 8 received FMT, and 9 underwent sham transplantation. Prior to the transplantation, all patients were treated with corticosteroids to induce remission of their acute flare-ups. The study found that none of the patients achieved more than 60% similarity with the donor microbiota after transplantation, indicating limited engraftment of the donor microbiota. Over the course of the study, there were 9 CD flares—6 in the sham group and 3 in the FMT group. Although the incidence of acute flares was lower in the FMT group, the difference was not statistically significant. However, a significant benefit of FMT over sham was observed in terms of CD Endoscopic Index of Severity (CDEIS) and C-reactive protein (CRP) levels. The FMT group showed a greater decrease in CDEIS compared to the sham group, and while CRP levels increased in the sham group, the FMT group did not show any increase in CRP[29]. A limitation of these findings was that the CDEIS in the sham group was already quite low at baseline, making it challenging to observe a significant further drop. As a result, no definitive conclusions could be drawn regarding the effectiveness of FMT in maintaining remission in CD.

In another clinical trial, He *et al*[30] investigated the role of multiple FMTs in inducing and maintaining clinical remission in CD complicated by inflammatory masses. The study included 25 patients with CD and inflammatory masses. Of these, 76% had ileum and colon involvement, 12% had ileal involvement, and 12% had colon involvement. After the first FMT, subsequent FMTs were administered at 3-month intervals. The primary route of administration was esophagogastroduodenoscopy to the duodenum, used in 23 of the 25 patients, while 2 patients received FMT *via* a tube inserted into the cecum during a colonoscopy. The initial FMT induced remission in 52% of patients. The proportion of patients achieving sustained clinical remission with repeated FMTs decreased over time: 48% at 6 months, 32% at 12 months, and 22.7% at 18 months. These findings suggest that while FMT demonstrated some efficacy in inducing clinical remission, its effect diminished despite repeated administrations. The study had several limitations, including the lack of a control group, small sample size, and the absence of endoscopic evaluation in any patient. Despite these limitations, the trial offered useful insights into the limited potential of FMT in treating complex CD cases.

In a study by Suskind *et al*[31], the role of FMT in active CD was investigated. The trial included 9 patients with active CD of mild to moderate severity, based on a Pediatric CDAI (PCDAI) score of 10–29. Prior to FMT, all patients were treated with rifaximin for 3 days and Miralax for 2 days. The FMT was administered *via* a nasogastric tube. Among the participants, only one patient had disease localized to the colon, while the remaining patients had multiple gastrointestinal sites affected, including the esophagus, stomach, duodenum, terminal ileum, and colon. Metagenomic sequencing revealed successful engraftment of donor microbiota in 7 out of 9 patients. At the 2-week follow-up, 7 out of 9 patients achieved clinical remission, and 5 out of 9 patients sustained remission at both 6 weeks and 12 weeks. Clinical response was measured by a significant decrease in PCDAI scores, which dropped from a baseline of 19.7 ± 7.2 to 6.4 ± 6.6 at 2 weeks and 8.6 ± 4.9 at 6 weeks. Minimal or no improvement was observed in patients who did not achieve successful

microbiota engraftment. While the study demonstrated potential benefits of FMT in managing active CD, it had several limitations, including the lack of a control group, small sample size, and the inclusion of antibiotics and laxatives prior to FMT, which may have influenced the outcomes. Additionally, the continuation of CD medications such as immunomodulators after FMT acted as a confounding factor in assessing the independent effect of FMT.

Wang *et al*[32] investigated the safety of FMT in patients with CD and found it to be a generally safe option. Among 139 patients who underwent a total of 184 FMTs with naso-jejunal tube or gastroscopic infusion, adverse effects were observed in 13.6% of patients. These adverse effects included increased frequency of defecation, mild abdominal pain, flatulence, hematochezia, and bloating, all of which occurred within the first month following FMT. No adverse effects were reported after the one-month mark. One patient developed herpes zoster, which was self-limiting. Of the 25 recorded adverse events, 84% (21/25) resolved without any treatment, while 16% (4/25) required medications. One patient required steroids due to persistent fever and was deemed to have experienced a failed FMT accompanied by a CD flare-up. The study also found a significant association between the method of fecal microbiota preparation and the occurrence of adverse effects. Patients who underwent manual methods of preparation had an adverse effect rate of 21.7%, compared to 8.7% for those who received FMT prepared using automated machine-operated purification methods. Despite this difference, the clinical remission rate was 56%, with no significant variation between the two preparation methods. Overall, the study concluded that FMT is a safe and effective treatment option for CD, with a reasonable clinical remission rate and manageable adverse effects.

Xiang *et al*[33] conducted a study involving 174 patients with CD to evaluate the efficacy of FMT, focusing on symptom improvement as the primary outcome. Most patients received FMT *via* mid-gut delivery methods, including endoscopy, naso-jejunal tubes, or transendoscopic enteral tubing. Only one patient underwent FMT *via* colonoscopy. The follow-up duration was 43 months. 109 patients received multiple FMTs. Overall, 43% of patients (76/174) showed a positive clinical response, and 20.1% (35/174) achieved sustained clinical remission. The study also observed that frozen FMT was associated with an 11.3% decrease in clinical response compared to fresh FMT, although the exact number of patients who received frozen FMT was not specified. Key limitations of the study included the absence of a control group, as well as the lack of biomarkers or endoscopic findings as objective targets for assessing treatment efficacy.

Yang *et al*'s RCT assessed the efficacy of FMT, comparing colonoscopy and gastroscopy as delivery methods[34]. 14 patients received FMT *via* colonoscopy, and 13 *via* gastroscopy, with a second FMT administered one week after the first. Clinical evaluations and serum testing to calculate the CDAI were performed at weeks 1, 2, 4, 6, and 8, with endoscopic evaluations conducted at week 8. Clinical remission was achieved in 66.7% (18/27) of patients, with no significant difference between the colonoscopy (64.3%) and gastroscopy (69.2%) groups. The overall clinical response rate was 77.8% (21/27), again showing no difference between the colonoscopy (78.6%) and gastroscopy (76.9%) groups. Notably, none of the patients achieved endoscopic remission at 8 weeks. Diarrhea was the most common adverse effect, occurring more frequently in the colonoscopy group (57.1%) compared to the gastroscopy group (14.3%). Aggravation of abdominal pain was reported in 21.4% of patients in the gastroscopy group and 14.3% in the colonoscopy group. Most adverse events resolved spontaneously within 24 hours. The study also found that clinical remission was more frequent in patients who received FMT from a related donor (73.7%, 14/19) compared to those who received FMT from unrelated donors (50%, 4/8), although this difference was not statistically significant. Key limitations of the study included a short follow-up duration and the absence of a control group without FMT treatment.

The findings of the above-mentioned studies are summarized in Table 4.

In the latest American Gastroenterology Association (AGA) clinical practice guideline on fecal microbiota-based therapies for select gastrointestinal diseases, the AGA advises against the use of conventional FMT for treating IBD, except as a part of a clinical trial[35].

Current evidence highlights the potential of FMT as a therapeutic option for CD, but its efficacy remains inconsistent and inconclusive. While some studies demonstrate promising clinical responses and remission rates, limitations such as small sample sizes, lack of control groups, short follow-up periods, and inconsistent methodologies hinder definitive conclusions. The variability in outcomes, including the diminished effects of repeated FMT and the inconsistent microbiota engraftment, underscores the need for standardized protocols and larger, well-controlled trials.

CONCLUSION

Multiple studies suggest a role for dysbiosis in gut microbiota in CD, but it remains unclear whether dysbiosis is a cause or consequence of the disease. FMT shows some promise as a therapeutic option for CD, with some studies reporting improved clinical responses and reduced disease activity. However, the evidence is limited by small sample sizes, methodological inconsistencies, and short follow-up periods. The variability in outcomes, including inconsistent microbiota engraftment and diminishing effects with repeated treatments, highlights the need for caution. Large-scale, RCTs are necessary to establish clear guidelines for FMT in CD treatment, including standardized protocols for delivery methods, donor selection, and follow-up duration. Further research is needed to understand the mechanisms behind FMT's effects and to identify biomarkers that can predict patient responses. While FMT may serve as a potential adjunctive therapy for managing CD, its widespread use cannot be recommended until more robust evidence is available to support its safety and efficacy.

Table 4 Role of fecal microbiota transplantation in Crohn's disease

Ref.	Type of study	Participants	Findings	Conclusion
Sokol *et al*[29]	RCT	8 received FMT. 9 received sham transplantation	Flare-up in 3/8 in FMT group. Flare-up in 6/9 in sham group. Higher decrease in CDEIS in FMT group	Difference in flare-up was not statistically significant. Limitations: Small sample size; low baseline CDEIS sham group
He *et al* [30]	Prospective cohort study	25 CD patients received multiple FMTs at 3-month interval. No control group	Remission induced in 52%. Sustained remission decreased overtime: 48% at 6 months. 32% at 12 months. 22.7% at 18 months	Some efficacy in inducing clinical remission. Effect diminished despite repeated administrations. Limitations: Lack of control group, small sample size, absence of endoscopic evaluation
Suskind *et al*[31]	Open label study	9 CD patients. No control group	7/9 achieved remission at 2 weeks. 5/9 showed persistent remission after 6 and 12 weeks	Potential benefits of FMT. Limitations: No control group, small sample size. Inclusion of antibiotics. Continuation of immunomodulators after FMT
Wang *et al*[32]	Prospective cohort study	139 CD patients. No control group	Remission in 56%. Adverse effects (AE) in 13.6% (25/139). AE in 84% resolved without treatment. AE in 16% needed medications. AE rate 217% in manual FMT preparation group *vs* 8.7% in automated machine-operated group	FMT generally safe. Automated purification method safer than manual method. Reasonable remission rate
Xiang *et al*[33]	Prospective cohort study	174 CD patients. No control group	43% achieved clinical remission. Sustained remission in 20.1% at 43 months. Frozen FMT showed 11.3% lower response compared to fresh FMT	Potential benefits of FMT in CD patients. Limitations: No control group. Lack of biomarkers. Lack of endoscopic findings
Yang *et al*[34]	Prospective cohort study	27 CD patients 14 received FMT *via* colonoscopy and 13 *via* gastroscopy. No control group. Follow-up period – 8 weeks	Clinical remission in 66.7%. No difference between colonoscopy (64.3) *vs* gastroscopy (69.2%) group. Clinical response in 77.8%. No difference between colonoscopy (78.6) *vs* gastroscopy (76.9%) group	Potential benefits of FMT. Limitations: No control group. Short follow-up period

RCT: Randomized controlled trial; FMT: Fecal microbiota transplantation; CDEIS: Crohn's disease endoscopic index of severity; CD: Crohn's disease; AE: Adverse effect.

FOOTNOTES

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MINIREVIEWS

Artificial intelligence-based apps for screening and diagnosing diabetic retinopathy and common ocular disorders

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Abstract

Artificial intelligence (AI), encompassing machine learning and deep learning, is being extensively used in medical sciences. It is slated to positively impact the diagnosis and prognostication of various diseases. Deep learning, a subset of AI, has been instrumental in diagnosing diabetic retinopathy (DR), diabetic macular edema, glaucoma, age-related macular degeneration, and numerous other ocular diseases. AI performs equally well in the early prediction of glaucoma and age-related macular degeneration. Integrating AI with telemedicine promises to improve healthcare delivery, although challenges persist in implementing AI algorithms, especially in deve-loping countries. This review provides a compre-

hensive summary of AI, its applications in ophthalmology, particularly DR, the diverse algorithms utilized for different ocular conditions, and prospects for the future integration of AI in eye care.

Key Words: Age-related macular degeneration; Alzheimer's disease; Artificial intelligence; Automatic retinal image analysis; Chronic kidney disease; Convolutional neural networks; Diabetic retinopathy; Diabetic macular edema; International council of ophthalmology; Machine learning; Massive training artificial neural networks; Natural language processing; OCT angiography; Optical coherence tomography; Vision transformers

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Core Tip: In this modern world, artificial intelligence-based algorithms have a definitive role in the early screening of different ocular diseases. Early screening helps in rapid referral and appropriate management to prevent sight-threatening complications. However, all said and done, it needs to be applied wisely to preserve the importance of human touch and empathy in clinical practice.

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INTRODUCTION

The estimated number of patients suffering from diabetes mellitus (DM) is expected to reach 642 million by 2040[1,2]. The ophthalmic complications of DM, namely diabetic retinopathy (DR) and diabetic macular edema (DME), are leading causes of blindness and visual disability. The increasing need for DR screening and overcoming issues associated with current screening methodologies have led to integrating artificial intelligence (AI) with screening protocols. The concept of AI was first discussed at a conference at Dartmouth College in 1956. However, many healthcare workers may feel overwhelmed as the technology is complex. Therefore, it is imperative to have a basic knowledge of the technical architecture used in AI. AI involves two phases: Training and validation, as well as testing. The training dataset typically includes clinical images and clinical data[3]. Thus, AI is a process in which a machine aids in recognizing specific patterns. It encompasses developing algorithms to represent the population for performance analysis. The research question and type of training dataset are crucial in algorithm development. Recently, AI has been projected to play a critical role in diagnosing and planning the management of patients with DR and other ocular diseases (Video).

METHODOLOGY

For this review, the most cited articles on AI in ophthalmology were searched in standard databases like Cochrane, EMBASE, Web of Science, Google Scholar and PubMed. The Reference Citation Analysis Tool was also applied to search for the keywords, and high-impact factor journal publications written in English were selected.

BASIC CONCEPTS IN UNDERSTANDING OF ARTIFICIAL INTELLIGENCE

Types of AI can be categorized as follows:

General Artificial Intelligence: Capable of performing tasks similar to human intelligence.

Narrow Artificial Intelligence: Specialized in specific tasks or domains.

Artificial Superintelligence: Superior to human intelligence in all aspects[4]. AI is continuously evolving and utilizes various techniques and algorithms to diagnose diseases. Commonly used techniques include natural language processing (NLP) methods and machine learning (ML) techniques. ML is divided into supervised learning (where training data is provided to the computer) and unsupervised learning (where the device creates its own algorithm without explicit training data).

Convolutional Neural Network (CNN) algorithms include LeNet, AlexNet, GoogLeNet, and ResNet. NLP involves processing unstructured data such as medical notes and journals and extracting information from them. ML is a technique for analyzing structured data (*e.g.*, genetic data and images), allowing computers to make diagnostic predictions through repeated learning from existing materials[5,6]. In ophthalmology, machine learning techniques are commonly utilized. These techniques involve computers repeatedly making predictions based on existing materials, particularly for automated analysis and classification of retinal images captured by optical coherence tomography (OCT)

or fundus photographs. Abràmoff *et al*[7] highlighted the role of an AI-based diagnostic algorithm in detecting DR in 900 diabetic patients with no history of DR. Ryu *et al*[8] developed an AI algorithm using OCT angiography images. The model achieved a sensitivity of 86%-97% and a specificity of 94%-99% for DR classification. The classification is slated for effective diagnostic workflow and detection of DR.

Deep learning (DL) models employ two algorithms: CNN, which categorizes retina images based on quantitative layers, and Massive Training Artificial Neural Networks[4]. In 2008, the United States Food and Drug Administration (FDA) approved the use of AI to detect brain tumours using MRI imaging. As far as the use of AI in retinal pathologies is concerned, various studies have been done. In a study by Ting *et al*[9], an AI algorithm detected DR using multiple retinal images. AI has a broad range of applications; in addition to diagnosis, AI can provide organizational assistance to surgical procedures to reduce manual workload[10].

CURRENT STATUS OF ARTIFICIAL INTELLIGENCE IN OPHTHALMOLOGY

A summary of various trials establishing the role of AI in ophthalmology is presented in Table 1. Recent advancements in ophthalmology have seen the adoption of innovative techniques to improve privacy and robustness, such as federated learning (FL), and address data scarcity through self-supervised learning[11,12]. New AI models, including DeepSeeNet and PredictNet, have emerged as promising tools for enhancing the detection and management of conditions such as age-related macular degeneration (AMD) and glaucoma[13,14].

The application of AI in ophthalmology has witnessed significant expansion, with tools providing real-time feedback for screening DR and refined models like DeepSeeNet demonstrating efficacy in predicting AMD progression[15,16]. Moreover, smartphone-based AI applications and AI-driven robotic surgery systems have emerged as notable developments, improving accessibility and precision in eye care[17,18]. Recent studies have introduced more advanced CNNs like EfficientNet, DenseNet, and vision transformers that have shown superior performance in image classification and disease detection in ophthalmology[19].

FL allows the training of AI models without sharing patient data and has been increasingly used to enhance privacy and improve the robustness of AI models in ophthalmology, for example in retinal imaging in relation to myopic maculopathy[20]. New self-supervised learning algorithms have been developed to improve AI performance in scenarios with limited labelled data, which is crucial for rare ophthalmic conditions such as ocular surface squamous neoplasia[21].

AI in DR has been enhanced with real-time diagnostic systems that provide immediate feedback, improving screening efficiency in clinical settings[22]. AI models like DeepSeeNet have been further refined to better predict the progression of AMD and the need for interventions like anti-VEGF therapy[13]. AI algorithms such as U-Net and PredictNet have improved accuracy in detecting glaucomatous optic neuropathy and predicting disease progression[14]. Novel AI approaches are now being used to diagnose and treat various disorders of the anterior segment[23]. Similar improvements are being noted in the prevention and treatment of common eye diseases as myopia, glaucoma, diabetic retinopathy, and cataracts. Medical resource allocation, risk prediction and early warning systems, illness screening and monitoring, ophthalmic data management, health education, and patient management are all significantly enhanced by AI[24].

Combining AI with telemedicine has become more prevalent, particularly in remote areas. This integration has helped reduce patient wait times and facilitate access to specialized care[25]. Significant progress has been made in developing AI-driven smartphone applications for eye screening, particularly useful in resource-limited settings[17]. AI-driven surgical supervision systems have fostered improvements in precision and control, enhancing outcomes in ophthalmic surgeries[26].

VARIOUS AI APPS IN DR

AI algorithms have a significant role in screening DR using fundus photographs. Recently, AI algorithms have been demonstrated to have a higher sensitivity and specificity in detecting referable DR than human graders. Recent advances in AI technology and the data-rich nature of the ophthalmology speciality have played a vital role in using AI in DR screening. Numerous deep learning models have outperformed feature-based machine learning methods (Table 2). The algorithms cleared by the FDA for clinical use in DR screening include IDx-DR, EyeArt, and AEYE Diagnostic Screening (AEYE-DS).

FDA-approved algorithms

The first FDA-approved AI algorithm, IDx-DR, utilized AI with a retinal camera and employed deep learning methods. It is used to determine the severity of DR and automatically refers cases with more than mild DR (mtmDR) to ophthalmologists while rescreening negative cases annually, boasting high sensitivity and specificity. IDx-DR's decision-making capability without an ophthalmologist's intervention makes it accessible to any healthcare professional[10].

The second AI system the FDA approved was EyeArt by Eyenuk Inc. (Los Angeles, CA, United States). EyeArt has a sensitivity of 96% and a specificity of 88% for diagnosing moderate DR and 92% and 94% for more severe cases of VTDR (vision-threatening diabetic retinopathy). In addition to its accuracy, this algorithm is incredibly efficient[27].

In November 2022, the FDA granted clearance to another algorithm developed by AEYE Health to screen for mtmDR, the AEYE-DS. It is the first fully autonomous AI diagnostic screening system, now integrated into commercially available

Table 1 Various trials on artificial intelligence in ophthalmology

Ref.	Data included	Results
Kanagasingam *et al*[43], 2018	A total of 216 patients, out of which 193 agreed to undergo eye screening. 386 images were evaluated by an AI-based system and by an ophthalmologist	Specificity: 92%; Positive predictive value 12%; Detection of false positive cases attributed to poor image quality
Arenas-Cavalli *et al*[44], 2022	Examination of 1123 diabetic eyes, utilizing a well-designed protocol endorsed by the Chilean Ministry of Health Personnel and Retina Specialists	Sensitivity: 94.6%; Specificity: 74.3%
Peeters *et al*[10], 2023	Analysis of a dataset comprising 16,772 cases of DR and 16833 cases of DME unique patient visits	Specificity for DR: 94.24%; Sensitivity for DME: 90.91%; Sensitivity in patients aged over 65 years: 82.51%
Brown *et al*[45], 2018	Utilization of 100 test images in Retinopathy of Prematurity using Inception–V1 and U-Net CNN	Predicted sensitivity: 100%; Predicted specificity: 94%
Ting *et al*[9], 2019	Incorporation of ten external datasets from various countries (Japan, United States, Hong Kong, Mexico, and Australia) employing the Deep Learning Algorithm VGG-19	Sensitivity in referable DR: 90.5%; Specificity in referable DR: 91.6%
Morya *et al*[52], 2021; Morya *et al*[53], 2021	World's first Smartphone based AI Annotation tool for grading multiple retinal images in a shortest span – quantitative and qualitative analysis	DR; AMD; Glaucoma; Retinitis Pigmentosa; CSR *etc.*

AI: Artificial intelligence; AMD: Age-related macular degeneration; CSR: Central serous retinopathy; DR: Diabetic retinopathy; DME: Diabetic macular edema.

Table 2 Various algorithms used in diabetic retinopathy as follows

Study conducted	Algorithms used	Identified and diagnosed
A retrospective study by Liu *et al*[46], 2022, using traditional fundus images	EfficientNet-B5	DME
A retrospective study by Dai *et al*[47], 2021	ResNet and Mask R-CNN	DR grading
A retrospective study by Lee *et al*[48], 2021	OpthAI, AirDoc, Eyenuk, Retina AI Health, Retmarker	Referable DR detection
A prospective study by Heydon *et al*[49], 2020	EyeArt v2.1	Referable DR detection
A prospective study by Gulshan *et al*[50], 2019	Inception-v3	Referable DR detection
Akram *et al*[51] proposed an automated module	MESSIDOR database used	Proposed an automated module for the grading of diabetic maculopathy

DME: Diabetic macular edema; DR: Diabetic retinopathy.

portable and table-top devices further enhancing the availability and accessibility of AI technology where it is required [28].

Research-based algorithms

SELENA+, a deep learning system, was developed in 2017 at the Singapore Eye Research Institute, Singapore. It was approved by the Singapore Health Service Authority to help in the national screening programme for Diabetic Retinopathy. It was used to detect vtDR (vision-threatening Diabetic Retinopathy) with considerable success[29].

MONA DR DME is a class 1 medical device recognized by the European Union Medical Device Directive that accurately predicts referable diabetic retinopathy, diabetic macular oedema and a combination of both. This software, requiring one fundus image per eye, efficiently reported three diabetic eye screening results with the image centred between the optic disc and macula. The program demonstrated high sensitivity and specificity in predicting both conditions[10] (Figure 1).

EyeWisdom V1, a diagnostic software employing DL algorithms, is designed to aid in diagnosing DR. A study was conducted to evaluate the practicality and safety of EyeWisdom V1 in diagnosing DR compared to manual grading. The study encompassed 1089 fundus images. For all cases of diabetic retinopathy, the sensitivity and specificity of EyeWisdom V1 were 98.23% (95%CI: 96.93%–99.08%) and 74.45% (95%CI: 69.95%–78.60%), respectively[30].

A novel retinal fundus image reading system was developed to provide large, high-quality data to create new screening algorithms. This 5-step system rates image quality, presence of abnormality, findings with location information, diagnoses, and clinical significance[31].

VeriSee DR is a deep-learning image assessment tool for diabetic retinopathy screening. VeriSee DR (Acer Inc., Taiwan). The software has been used in Taiwan and Thailand. It utilizes CNN for training algorithms for DR screening. It

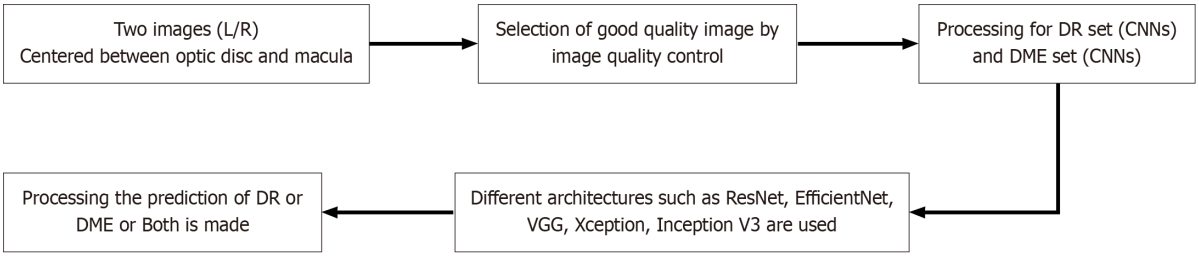


Figure 1 Artificial intelligence algorithm for diabetic retinopathy prediction. CNN: Convoluted neural network; DME: Diabetic macular edema; DR: Diabetic retinopathy; L/R: Left/Right; VGG: Visual geometry group.

was used to diagnose referable DR according to the International Clinical Diabetic Retinopathy Disease Severity Scale. Every image was gradable with a maximum sensitivity of 95.7%, and maximum specificity of 94.2% using various camera models[32].

AI algorithms have utilized the Kaggle public dataset developed to detect severe DR using colour fundus photography. A study wherein > 4000 photographs were selected for lesion annotation and the Inception V3 structure employed as the categorization algorithm, the findings demonstrated enhanced performance with 896-pixel input images, including increased sensitivity, specificity, and area under the receiver operating characteristic curve. The study concluded that this artificial intelligence-driven system can enhance the accessibility and efficacy of severe DR screening [33].

An innovative algorithm was developed for diabetic retinopathy grading training of junior ophthalmology residents and medical students. A total of 520 fundus photographs were included in this study. Photographs were divided into eight groups, with 65 images for each group[34]. Thus, this AI not only grades DR accurately but is also being used to train humans in doing so.

In 2016, another deep-learning system was introduced by Gulshan *et al*[35] It was developed at Google Inc., United States. It is a CE-marked medical device used to detect referable/non-referable DR.

Retmarker DR software, a deep learning system, was developed at the University of Coimbra, Portugal. It is a CE-marked medical device used for disease/no disease grading and detection of microaneurysm turnover. It also has the capability to compare current and previously captured images, enabling the assessment of disease progression[4].

Other AI techniques, such as morphological component analysis combine k-nearest neighbour algorithms and AI-recognised cues to achieve fast and accurate optic disc detection[36]. Morphological Component Analysis, has shown very high specificity, ranging from 97.45% to 97.53%, as reported in a study by Imani *et al*[37].

Considering more than minimal DR, which includes microaneurysms, hard exudates, retinal haemorrhages, cotton wool spots, and DME, AI implemented on portable devices and smartphone attachments in primary care settings demonstrate sufficient image quality for algorithmic assessment[38].

Recent advancements include a novel AI network approach combining segmentation and classification tasks. Morphological features are utilized for segmentation, identifying various OCT pathologies like DR, choroidal neovascularization, vitreomacular traction, drusen, macular hole, and serous retinopathy to enable early detection of subtle features and appropriate referral[38].

WHY IS THERE A NEED FOR AI IN DR?

Al-based diagnostic systems offer numerous advantages, including rapid processing speeds, reliable outcomes, and the capability to reduce interobserver variability. These technologies facilitate the screening of diabetes patients on a larger scale and in resource-limited environments by enabling the analysis of substantial volumes of images in a significantly shorter time frame compared to human specialists. The grading of retinal images in diabetic patients through fundus examination or colour fundus photography typically requires specialised retinal specialists, whose numbers are limited, especially in developing countries. Consequently, introducing AI systems has alleviated some of the challenges associated with manual grading, which is both expensive and labour-intensive (Figure 1).

CHALLENGES IN IMPLEMENTING AI

The scientific community reports that most algorithms have not been developed into software for primary or secondary care levels. Another factor is that while most algorithms focus on reporting DR, consideration of both DR and DME is essential and relevant. The real-world use of AI in DR can be challenging due to the technicalities of the technology, especially in the developing world[39]. Also, AI grading of DR in patients with significant cataracts and poor media clarity may be complex. The medicolegal issues associated with the inadvertent wrong diagnosis using AI can be a problematic situation for authorities and the medical fraternity. The application of FL can be a possible solution to address such problems.

There is an urgent need for widespread and accessible DR screening tools for individuals with diabetes mellitus. The same has been emphasized by the International Diabetes Federation, the International Council of Ophthalmology, the World Council of Optometry, and the International Agency for the Prevention of Blindness. The use of AI can play a significant role in making the screening and diagnosis of DR accessible[10].

Telemedicine alongside AI

Telemedicine, coupled with AI, can improve the health status of patients by exchanging medical information electronically between sites. In areas lacking health workers, telemedicine can facilitate the distribution of healthcare to remote regions, reducing waiting times for both patients and clinicians. Additionally, DL algorithms have been applied as visual impairment screening tools, aiding in referring patients to tertiary eye centres based on visual impairments[30]. Community-based teleophthalmology DR screening has been a useful tool in screening of referable DR in India. The MII RetCam (MII Ret Cam Inc, Coimbatore, India) and the Remidio fundus-on-phone (Remidio Innovative Solutions Private Limited, Bengaluru, India) are economical and portable, and several studies have shown their advantage in limited resource settings[39-41].

AI-driven robots

AI-driven robots are valuable and time-saving tools to enhance and improve patient health while making healthcare cost-effective. They are currently utilized in rehabilitation and physical therapy to enhance patients' motor and functional capabilities. Additionally, they find applications in telesurgery and geriatric care, such as in countries like Japan, where Eldocare robots are utilized. Furthermore, they can be employed in new drug development processes to detect adverse effects of medications[18]. However, they currently have limited applicability in the field of ophthalmology. More research and development is needed in the field of robotics driven by AI to devise novel technologies that deliver vision therapy, monitor medication compliance, and provide assistive support to persons having visual impairment, including amblyopia and visual field defects.

Healthcare AI companies

Several healthcare AI companies have developed various software for disease detection. For instance, Viz.ai introduced an Aneurysm detection software in 2018, Beth Israel Medical Centre developed an AI-powered microscope for detecting blood infections in 2017, and VirtuSense launched Movement Anomaly Detection software in 2012. Despite embodying significant advancements, these companies primarily work on a for-profit basis thereby raising concerns about data security and privacy[24]. Pooled multiethnic datasets being used to train AI are commercially marketed and thereby subject to the same security concerns[42].

Main challenges and concerns in implementing AI

The lack of regulations and guidelines for the application and creation of AI poses significant challenges. Further research is needed to develop AI ethically and ensure its appropriate use. Additionally, AI should be tailored and adapted based on different regions' demographics and healthcare systems[38].

Several AI algorithms used in various studies are based on traditional fundus imaging (TFI) or smartphone-based fundus images, especially in DR and other retinal disorders[43-51]. Morya *et al*[52,53] have analysed various studies in DR and AMD and commented that bias related to sampling, prejudice for example in the context of suspicious optic discs, measurement bias related to instrumentation, a wrong choice of software algorithm and concerns related to quality control of images utilized, all constitute the challenges being faced in the AI world today[52,53].

OTHER USES OF AI IN OPHTHALMOLOGY

In healthcare, AI has the potential to improve the outcomes of diseases. Data from electronic health records has shown that it reduces readmissions, particularly in patients with diabetes, heart disease, and cancer.

In chronic and non-reversible macular disease, AMD, AI can detect early stages automatically by detecting drusen or fluids. Some algorithms can predict the early onset of AMD and the need for anti-VEGF treatment[54]. Morya *et al*[52,53] developed the World's first smartphone-based AI annotation tool for grading multiple retinal images of 15 common disorders using a qualitative and quantitative deep–learning module. This tool had flexibility, portability, and high accuracy in image annotation. Thus, AI can help in identification and documentation of retinal lesions to guide treatment decisions.

DeepSeeNet, developed by Peng and his collaborators, is an algorithm that assesses the severity of AMD with good precision and accuracy[16]. Recently used algorithms include temporal deep learning models using OCT images, self-supervised non-parametric instance discrimination AI using TFI, and SLIVER-net models using 3d-OCT images for the detection of AMD, and choroidal neovascularization in AMD[55].

A CNN combined with a patch and image-based method has reported high accuracy in diagnosing Retinal Vein Occlusion. Similarly, significant advances in OCT imaging are notable in pathologic myopia, with a renewed grading system aiding in the detection of myopic maculopathy.

Many studies based on two-level sorting have proven effective in diagnosing Retinopathy of Prematurity (ROP). I-ROP DL has the potential to assess disease progression and regression of ROP. Additionally, the patient's response to treatment can also be analyzed[4].

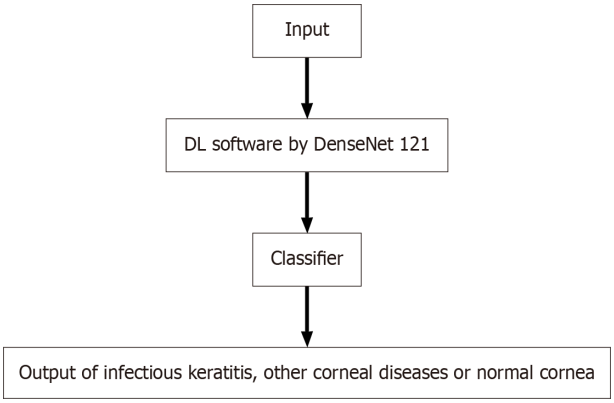


Figure 2 Artificial intelligence algorithm for corneal disorders. DL: Deep learning.

Automatic artificial intelligence segmentation using OCT measures glaucoma patients' retinal nerve fibre and ganglion cell layer. Akter and colleagues developed the first algorithm in 2022[56]. Algorithms used include FusionNet in detecting glaucomatous optic neuropathy, U-Net and PredictNet in predicting glaucoma incidence and progression, ResNet 50 in detecting primary open angle glaucoma among patients with ocular hypertension, and 3d-ResNet-34 and 3d-ResNet-50 in suspected primary angle closure glaucoma with narrow iridocorneal angles and anterior synechiae[20].

In diagnosing dry eye, a DL approach is used to segment Meibomian glands digitally, achieving 95.6% meiboscore accuracy. The accuracy for segmentation of the eyelid and atrophy has been reported as 97.6% and 95.4%, respectively [55].

The Congenital Cataract Guardian System has been incorporated in congenital cataracts, exhibiting high sensitivity and specificity. This system, a smartphone app, comprises three function modules: Prediction, dispatching, and telehealth. Algorithms such as DeepLensNet, ResNet50, XGBoost Classifier, Global-local attention network, Random forest, and adaptive screening methods are utilized for diagnosing and quantitatively classifying age-related cataracts. AI is also employed in Phacoemulsification cataract surgery, utilizing Faster Region-based CNN[20].

Keratoconus, which can result in irreversible vision loss, can be detected using AI to identify subclinical keratoconus, which is crucial for improving visual prognosis. The algorithm for diagnosing subclinical keratoconus, BESTi, has demonstrated high sensitivity and specificity[55].

MobileNet is employed to differentiate between bacterial keratitis (BK) and fungal keratitis (FK)[57,58]. Random Forest is another algorithm used for differentiating BK, FK, and viral keratitis[59] (Figure 2).

Specular microscopy images have been instrumental in developing artificial intelligence algorithms to differentiate between normal and pathological corneas for corneal grafting[60,61].

U-Net and DenseNet networks are used. Optic atrophy and optic disc drusen were observed, with 96.4% sensitivity and 84% specificity in detecting papilloedema and normal ONH.

AI LIMITATIONS

One primary consideration is the lower quality of ocular fundus photographs in older populations, particularly in teleophthalmology, where image quality is inversely related to age[62]. Implementation of AI carries a risk of bias, emphasizing the need for continuous monitoring and regulatory guidelines[63]. AI algorithms have been associated with high false-positive rates, with data availability lacking for rare diseases such as eye tumours and common diseases like cataracts not routinely imaged[64]. While AI algorithms are prevalent in developed countries, there's a pressing need for their adoption in developing countries to address the scarcity of clinicians and high costs. More extensive training on image data is necessary to improve the sensitivity and specificity of AI[65]. Data sharing poses ethical and legal challenges. Federated Learning, where data resides in various institutions without centralization, can address these issues, ensuring patient privacy while enhancing AI robustness[66]. The current cost of developing AI algorithms is very high, and there are challenges like data breaches, data theft, and lack of transparency regarding how autonomous machine learning works, leading to reservations about this technology[67]. As ophthalmic images especially pertaining to the retina can be linked to several medical diseases (Table 3), AI acquisition of these images is a black box which can have unprecedented ramifications[68-71].

CONCLUSION

AI has undergone an industrial revolution recently, particularly in processing input data through deep learning without human intervention. It has demonstrated high accuracy in various fields, including medical image analysis. AI has been employed in analyzing ocular images captured by OCT, OCT Angiography, and fundus photographs. AI shows promise for long-term integration with telemedicine. The use of AI is imperative to improve the screening efficiency of DR in

Table 3 Artificial intelligence use in non-ophthalmologic disease

Diseases	Artificial intelligence algorithm
Autism spectrum disorder[68]	DL model based on OCT images and automatic retinal image analysis
Chronic kidney disease[69]	Elevated urine albumin/creatinine ratio associated with reduction in retinal and choroid vasculature density in OCT or OCT angiography studies
Iron deficiency anemia[70]	Lower retinal vessel density and reduced vessel light reflectance observed in OCT images
Intracranial hypertension[71]	Brain and Optic nerve study (BONSAI) AI, U-Net and DenseNet networks used and Papilledema, optic atrophy and optic disc drusen observed, with 96.4% sensitivity and 84% specificity in detecting papilloedema and normal ONH
Alzheimer's disease [62]	DL model using retinal images showed 83.6% accuracy, 93.2% sensitivity, 82.0% specificity, and an AUROC of 0.93 for detecting Alzheimer's disease-dementia

AI: Artificial intelligence; AUROC: Area under receiver operating characteristic curve; DL: Deep learning; OCT: Optical coherence tomography; ONH: Optic nerve head.

addition to other diseases like AMD, ROP, and Glaucoma. Additionally, AI algorithms aid in understanding the relationships between systemic diseases and ocular conditions. To achieve a broader acceptance, methodologies must be developed to integrate AI into decision-making processes effectively. Incorporating AI into healthcare is imperative for improving patient outcomes through early diagnosis and intervention, leading to cost-effective, streamlined processes. However, implementing AI software can present medical and ethical challenges. The use of AI may be associated with data privacy issues and have to be addressed promptly. AI should be viewed as a tool to assist practitioners.

FOOTNOTES

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MINIREVIEWS

Endoscopic ultrasound-guided radiofrequency ablation of pancreatic tumors: Current status and future perspectives

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Abstract

Pancreatic neoplasms present a significant therapeutic challenge due to their complex anatomy and poor prognosis. In recent years, endoscopic ultrasound guided radiofrequency ablation (EUS-RFA) has emerged as a promising minimally invasive therapeutic option, aiming to provide targeted treatment with improved patients' outcomes. This review aims to shed light on current evidence about the efficacy, safety, and clinical outcomes of EUS-RFA in the management of pancreatic neoplasms. We conducted a comprehensive search of literature, reviewing studies that document the application of EUS-RFA in pancreatic masses. The key metrics for efficacy included tumor size reduction, pain relief, and overall survival, while safety outcomes focused on procedural complications and post-operative recovery. EUS-RFA has demonstrated potential in effectively managing both benign and malignant pancreatic neoplasms, with several studies reporting significant reductions in tumor size and symptomatic relief. The technique is associated with a favorable safety profile, characterized by a low incidence of major complications. EUS-RFA represents a valuable addition to the therapeutic arsenal for pancreatic neoplasms, offering a viable alternative to

surgical interventions, especially in patients with contraindications for surgery. Further studies are needed to establish standardized protocols and long-term outcomes, enhancing its applicability and success in clinical practice.

Key Words: Endoscopic ultrasound; Radiofrequency ablation; Pancreatic tumors; Safety; Efficacy

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Core Tip: Endoscopic ultrasound-guided radiofrequency ablation has emerged as a promising minimally invasive approach for managing pancreatic tumors, providing a valuable alternative for patients who are poor surgical candidates. It effectively achieves significant tumor size reduction, symptom relief, and, in selected cases, prolonged survival, especially in pancreatic neuroendocrine tumors and cystic lesions. Despite a favorable safety profile, including low rates of major complications, standardization of protocols and further technological advancements such as artificial intelligence integration and combination therapies are essential for optimizing treatment outcomes and broadening clinical applicability.

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INTRODUCTION

Pancreatic cancer is one of the most lethal malignancies worldwide, with the highest incidence rates in developed countries. It is anticipated that the incidence of pancreatic cancer will increase in the coming decades, making it a growing public health concern[1,2]. The majority of patients are diagnosed with advanced disease, and the survival rate for pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, remains dismal, with a five-year survival rate of less than 10%. This is largely due to the inability to detect the disease early and the absence of effective treatment options once it reaches advanced stages[3].

Pancreatic neuroendocrine tumors (PNETs) and pancreatic cystic lesions (PCLs), while less common, also represent significant clinical challenges and are also associated with high morbidity and mortality. These tumors often present at advanced stages with nonspecific symptoms, which makes them difficult to diagnose early and complicates their treatment options.

Surgical resection remains the gold standard for pancreatic cancer, but many patients are not candidates for surgery due to poor functional status, advanced age, or comorbidities. Moreover, tumors located near critical vasculature or those that are borderline resectable pose additional challenges, highlighting the need for alternative treatment strategies[3,4].

One such emerging strategy is endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA), a minimally invasive procedure that uses thermal energy to destroy tumors. It combines the precision of EUS with the cytotoxic potential of thermal ablation. This technique has shown promise in a variety of pancreatic tumors, including PNETs, PCLs, and PDAC, especially in patients who are not surgical candidates. Recent studies have demonstrated the efficacy of EUS-RFA in achieving tumor shrinkage allowing for potential downstaging, symptom relief, and in some cases, prolonged survival. However, despite these promising outcomes, there remain significant gaps in understanding the optimal indications, procedural standardization, and long-term effectiveness of EUS-RFA[5].

This review aims to evaluate the current evidence surrounding EUS-RFA for pancreatic tumors, discuss its clinical applications, compare it with other therapeutic modalities, and provide a perspective on future directions for this promising technology.

MECHANISM OF ACTION OF EUS-GUIDED RFA

Biophysical principles of RFA

RFA uses high-frequency electrical energy (350-500 kHz) to generate heat in the targeted tissue. The process of ablation involves the conversion of electrical energy into thermal energy, causing the protein molecules within the tissue to denature and leading to coagulative necrosis. The basic principle of RFA is based on the thermal effects that occur when the tissue reaches temperatures of 60-100 °C, which is sufficient to induce irreversible damage to the cellular structure, leading to cell death. The degree of cellular destruction depends on both the peak temperature achieved and the duration of heat exposure. Above 60 °C, irreversible protein denaturation occurs rapidly, while temperatures above 100 °C can result in tissue vaporization and carbonization, which may limit the conduction of further energy[6]. RFA creates a thermal ablation zone characterized by three distinct areas:

Central necrotic zone: Directly affected by the highest temperatures, where immediate tissue coagulation and necrosis occur.

Transitional zone: Experiences lower temperatures that cause partial tissue damage, potentially leading to delayed cellular death *via* apoptosis.

Peripheral zone: Least affected area that may suffer secondary damage due to heat propagation, influencing tissue integrity and recovery.

A major factor influencing the efficiency of RFA is the heat sink effect, which occurs when blood vessels nearby dissipate heat, reducing the temperature of the tissue and potentially impairing the efficacy of the treatment by reducing the ablation zone. This effect can be especially problematic in highly vascularized tumors, such as those in the pancreas, where careful consideration of the device settings and procedural technique is required to achieve optimal results[7].

EUS-RFA device types and settings

The success of EUS-RFA is largely dependent on the technology used, with several devices currently available for clinical practice. The two main types of devices used are monopolar and bipolar probes, each offering distinct advantages. Devices designed with internal cooling or modified electrode geometry aim to mitigate this. Moreover, real-time temperature monitoring during EUS-RFA is an evolving area aimed at enhancing safety and control of the ablation process. Recent preclinical models have demonstrated that combining RFA with adjunctive agents or varying waveform energy delivery may optimize lesion creation.

Monopolar systems

The Habib™ EUS-RFA probe is one of the most widely used monopolar probes. It consists of a thin needle electrode that can be inserted into the tumor through a 19-G endoscopic needle, offering precision and minimal tissue damage during insertion.

The EUSRA probe is another widely used device that enables controlled ablation of pancreatic tumors with adjustable electrode exposure lengths, allowing for fine control of the ablation zone.

Bipolar systems

The Hybrid Cryotherm Probe combines RFA with cryotherapy, a technique that uses cooling and heating to enhance the ablation effect. This hybrid approach is particularly useful in treating large or centrally located tumors.

Ablation settings typically range from 10 to 60 W, with single or multiple 10-20 second cycles depending on tumor size and location. The choice of probe, power setting, and ablation duration depends on the tumor's characteristics and location[6].

Monopolar systems like the Habib™ EUS-RFA and the EUSRA Probe are favored for their precision and minimal tissue disruption during insertion. This device allows for precise control of the ablation area, suitable for targeting small to medium tumors with clear boundaries.

Bipolar systems, such as the Hybrid Cryotherm Probe, offer advantages in managing larger or vascular-rich tumors by combining RFA with cryotherapy. This method reduces the heat sink effect, which is crucial in highly vascularized areas like the pancreas[6,7].

Clinical applications: (1) Monopolar probes: Ideal for precise, small-scale ablations where the risk of damaging surrounding tissues is minimal. Commonly used in well-demarcated lesions away from major blood vessels; and (2) Bipolar probes: Better suited for complex cases with larger or irregularly shaped tumors or those located near critical structures, as they allow for a more controlled and uniform thermal spread[7]. EUS-RFA is frequently compared to other local ablation modalities, as summarized in Table 1.

Comparison of EUS-RFA with other local ablation modalities

While EUS-RFA has shown considerable promise, direct comparisons with other local ablation modalities remain limited. Microwave ablation offers deeper tissue penetration and faster energy delivery, which may be advantageous in larger lesions, but it often lacks the precise targeting that EUS guidance provides[8]. Cryoablation offers a favorable safety profile due to controlled tissue freezing, yet may require multiple sessions for efficacy and carries the risk of cryoshock[9]. Irreversible electroporation is a non-thermal ablation method that preserves vascular structures and avoids the heat sink effect, making it suitable for tumors near critical blood vessels. However, its high cost and limited availability can be barriers to widespread use[10]. Future head-to-head trials are needed to guide modality selection based on tumor characteristics, location, and patient-specific factors.

CLINICAL INDICATIONS FOR EUS-RFA

PNETs

PNETs are one of the most common indications for EUS-RFA (Figure 1). Surgical resection remains the standard of care for PNETs, but EUS-RFA offers an alternative approach for patients with smaller lesions, especially functional tumors like insulinomas. It is also a good option for patients who are poor surgical candidates due to age or comorbidities, or patients

Table 1 Comparison of endoscopic ultrasound-guided radiofrequency ablation with other local ablation techniques

Technique	Mechanism of action	Advantages	Disadvantages (complications)
Endoscopic ultrasound-guided radiofrequency ablation	Thermal ablation *via* high-frequency current	Minimally invasive, precise targeting, low morbidity	Risk of pancreatitis, limited penetration depth
Microwave ablation	Electromagnetic energy creates heat	Faster ablation, deeper penetration	Less precise targeting, potential for heat sink effect
Cryoablation	Freezing-induced necrosis	Lower pain, preservation of tissue integrity	Requires multiple sessions, risk of adjacent organ injury
Irreversible electroporation	Non-thermal, disrupts cell membranes	No heat sink effect, preserves vascular structures	Expensive, limited availability

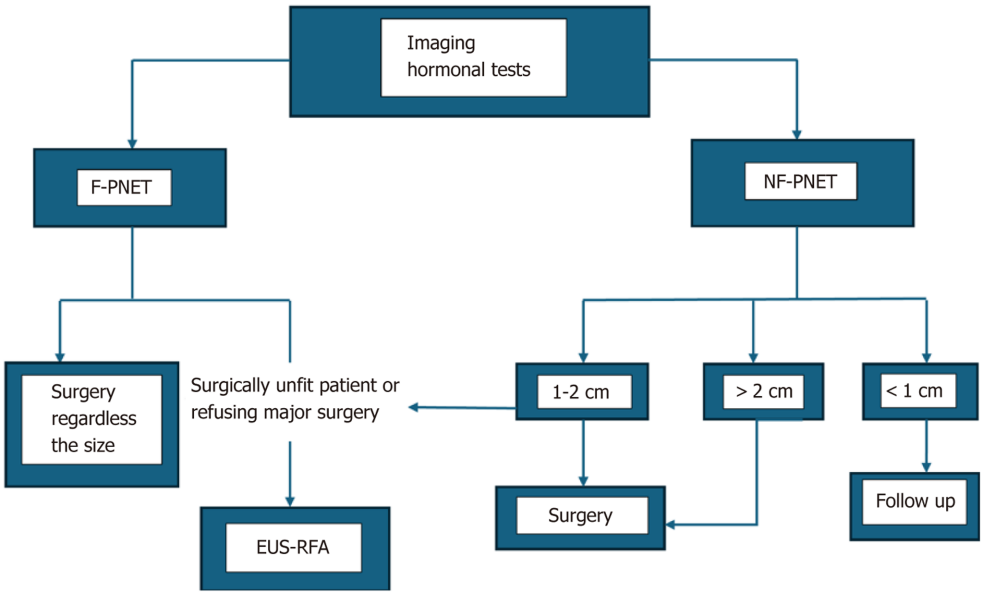


Figure 1 Management of pancreatic neuroendocrine tumor. This flowchart outlines the standard management options for pancreatic neuroendocrine tumor based on size, symptoms, and surgical eligibility. PNET: Pancreatic neuroendocrine tumor; F-PNET: Functional pancreatic neuroendocrine tumor; NF-PNET: Nonfunctional pancreatic neuroendocrine tumor; EUS-RFA: Endoscopic ultrasound guided radiofrequency ablation.

refusing major surgery. The success rates for insulinoma ablation with EUS-RFA are impressive, with studies showing 85%-95% resolution of symptoms[4].

For nonfunctional PNETs, especially those < 2 cm, EUS-RFA offers an excellent palliative option, achieving significant tumor reduction and potentially prolonging patient survival. In cases where surgical resection is not feasible, EUS-RFA can provide a less invasive means of controlling tumor growth and relieving symptoms related pain and compression of surrounding structures[5,11].

PCLs

PCLs, particularly intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, represent a growing area of focus for EUS-RFA. These lesions can be difficult to manage, especially in patients with high-risk features such as mural nodules or growing lesions. Traditionally, surgical resection has been considered the gold standard for these cysts; however, the increasing evidence supporting the use of EUS-RFA shows that it can be a less invasive option for patients with small, symptomatic cysts, especially those located in the head region.

Studies show that RFA of PCLs can result in up to 70% cyst resolution, significantly reducing the need for repeat surgical interventions. When mural nodules or high-risk features are present, EUS-RFA may offer a valuable bridge to surgery, shrinking the lesion and making it more resectable[12].

PDAC

EUS-RFA has been increasingly considered for PDAC, particularly in cases where tumors are classified as locally advanced or borderline resectable. The strategic use of EUS-RFA offers several clinical benefits:

Locally advanced tumors: For tumors that cannot be surgically removed without significant risk of morbidity or incomplete resection, EUS-RFA can be utilized to enhance the efficacy of chemotherapy. By reducing the tumor mass and disrupting the stromal barrier, EUS-RFA may improve chemotherapeutic drug delivery and absorption. Moreover, this technique has been associated with significant pain reduction, directly impacting patient quality of life by targeting

nerves involved in pain transmission within or adjacent to the tumor.

Borderline resectable PDAC: In borderline resectable cases, EUS-RFA can play a crucial role in downstaging the tumor, potentially converting an inoperable tumor into a surgically manageable condition. By reducing tumor size and involvement with critical vascular structures, EUS-RFA increases the likelihood of a successful surgical resection with negative margins, which is a key determinant of long-term survival[13]. However further prospective studied are needed to verify the efficacy of RFA in downstaging of PDAC.

Pancreatic metastases

While the application of EUS-RFA in primary pancreatic tumors is well-documented, its role in managing pancreatic metastases from other primary cancers like renal cell carcinoma (RCC) and colorectal cancer (CRC) is emerging as a promising therapeutic option. Initial studies and clinical reports suggest that EUS-RFA can effectively target and ablate metastatic lesions within the pancreas, offering a minimally invasive alternative to systemic chemotherapy or major surgery, which can be particularly advantageous in patients burdened with significant comorbidities or those who have previously undergone multiple treatments.

Metastatic RCC: RCC metastases to the pancreas are often resistant to chemotherapy, making local control strategies like EUS-RFA valuable. EUS-RFA can provide localized tumor control without the systemic side effects associated with conventional treatments[14].

Metastatic CRC: For CRC metastases, which often present as multiple small lesions within the pancreas, EUS-RFA can be used to ablate lesions that are not amenable to resection or when patient preference dictates a less invasive approach[15].

CLINICAL OUTCOMES OF EUS-RFA

Evidence from PNETs, PCLs, and PDAC

The success of EUS-RFA in clinical practice is evidenced by a growing body of research, particularly in PNETs and PCLs, where significant reductions in tumor size, symptom relief, and improved quality of life have been reported.

PNETs: Complete ablation has been reported in up to 87% of cases, with some studies indicating a near 90% recurrence-free survival at 12 months. These statistics suggest a robust potential for EUS-RFA not only as a palliative measure but also as a curative approach in selected cases. Detailed longitudinal studies have shown that symptom relief, particularly in insulinomas, correlates strongly with reduced hospitalizations and improved patient-reported outcome measures[4, 16].

PDAC: The efficacy of EUS-RFA for PDAC is more limited and more challenging due to the aggressive nature of the tumor and its dense vascular environment. However, early studies have shown promising results in terms of tumor necrosis and pain management which is valuable for improving patient quality of life. Combined treatment strategies such as EUS-RFA + chemotherapy showed improved progression-free survival[17] (Table 2).

Post-treatment surveillance

Standardized surveillance protocols are crucial for monitoring post-ablation outcomes and early detection of recurrence. Follow-up typically includes cross-sectional imaging such as contrast-enhanced CT or MRI at 1, 3, and 6 months post-procedure, followed by annual scans if stable[18]. For PNETs, periodic hormone panels and chromogranin A levels are useful adjuncts. In PCLs, EUS may be repeated to assess cyst resolution or residual septations[19]. Developing evidence-based surveillance pathways tailored to tumor type, size, and ablation extent will improve consistency in post-RFA care.

SAFETY AND COMPLICATIONS

Short-term complications

The most common short-term complication associated with EUS-RFA is post-ablation pancreatitis, which occurs in approximately 7%-10% of cases. This complication is typically mild and resolves with conservative management, such as fasting and intravenous fluids. However, in some cases, it can lead to significant morbidity, requiring more intensive management. The risk of pancreatitis is higher in tumors located near the pancreatic duct or those with larger volumes of treated tissue. Preventive strategies, including the use of preprocedure intake of NSAID or prophylactic pancreatic duct stenting, have been shown to reduce the risk of pancreatitis in high-risk patients[12,16].

Other short-term complications include **a**bdominal pain, bleeding, and infection. These are generally transient and managed conservatively. Bowel perforation and gastric ulcers are rarer but more serious complications that can occur, especially in tumors located near the duodenum or gastric wall. The incidence of major complications is typically low, with studies showing rates of around 1% or less[16].

Table 2 Outcomes of endoscopic ultrasound-guided radiofrequency ablation for pancreatic tumors

Tumor type	Technical success (%)	Complete ablation (%)	Symptom relief (%)	Major complication rate (%)
Neuroendocrine tumors	98	87	95	5
Pancreatic cystic lesions	95	70	60	7
Pancreatic ductal adenocarcinoma	90	30	50	10
Metastases	85	50	65	8

Long-term complications

Long-term complications of EUS-RFA are less well documented due to the relative novelty of the technique. However, **c**hronic pain or recurrence of treated tumors can occur in certain cases particularly in patients with repeated or high-intensity ablations. Recurrence is more common in tumors that are not completely ablated, in larger tumors where the energy used during the procedure might not have been sufficient to destroy the entire tumor mass or in aggressive tumor subtypes. For PNETs, the recurrence rate is generally low (around 10% at 12 months), with higher recurrence seen in histopathologic stage G2 tumors, larger tumors or those located near major blood vessels[12].

Pancreatic fistula formation is another potential long-term complication, particularly in cases where there is significant pancreatic duct injury during the procedure. This can result in prolonged drainage or the need for surgical intervention in rare cases. Advances in imaging and the use of real-time monitoring during the procedure have significantly reduced this risk[20].

Economic and medical burden

In addition to clinical risks, the economic burden associated with EUS-RFA is an important consideration. Although EUS-RFA may reduce hospitalization and surgery costs in the long term, the upfront expense of the procedure, specialized equipment, and operator expertise can be substantial. Cost-effectiveness studies are still limited, but early data suggest that EUS-RFA may be more economical in selected patient groups, particularly those unfit for surgery or with localized, small-volume disease. Further analysis comparing direct and indirect healthcare costs across treatment modalities is warranted to better understand the overall financial impact on patients and healthcare systems[21].

FUTURE PERSPECTIVES

Standardization of EUS-RFA protocols

One of the key limitations of EUS-RFA is the lack of standardization in procedural techniques, including variations in electrode selection, energy settings, and ablation duration. This lack of uniformity makes it challenging to compare outcomes across studies. Standardized guidelines for optimal energy settings, ablation zones, and procedural steps are needed to improve consistency and maximize the success rate of the procedure. Ongoing multicenter trials and expert consensus meetings are likely to address these gaps and provide a framework for practice.

The development of protocols for patient selection, particularly focusing on tumor size, location, and vascular involvement, will also be critical. Further research into biomarkers that predict response to RFA, such as tumor-specific antigens or genetic markers, will help guide patient selection and improve treatment outcomes.

Advancements in technology

There have been significant advances in ablation technology, with newer devices offering enhanced precision and minimized collateral damage. The development of multi-needle probes and cooled-tip RFA devices is particularly noteworthy. These devices allow for more controlled and uniform energy delivery, reducing the risk of complications such as thermal injury to adjacent structures[13].

Another exciting area is the integration of robotic systems and artificial intelligence (AI) into EUS-RFA. AI is increasingly being integrated into endoscopic systems to enhance image interpretation, tumor detection, and procedural planning. AI algorithms can assist operators in accurately identifying ablation zones, predicting the optimal trajectory for probe insertion, and dynamically monitoring the treatment response in real time[22,23]. Robotic-assisted EUS may also offer improved precision and control, minimizing operator-dependent variability and enhancing procedural reproducibility, particularly in difficult anatomical locations[24].

Combination therapies

Combination therapies are expected to play a significant role in the future of EUS-RFA for pancreatic cancer. Combining EUS-RFA with chemotherapy or immunotherapy has shown potential in preclinical studies and early-phase clinical trials. For example, combining gemcitabine or FOLFIRINOX with EUS-RFA could not only shrink the tumor but also increase the efficacy of chemotherapy by improving tumor vascularity and drug delivery to the tumor site[17].

In addition, the combination of EUS-RFA and immune checkpoint inhibitors is an exciting area of investigation. Tumor necrosis induced by RFA can release tumor antigens, which, when combined with immune checkpoint inhibitors, could trigger an immune response against the tumor. This synergy between local and systemic therapies could be a game-

changer in the management of locally advanced pancreatic cancer[25].

CONCLUSION

EUS-RFA represents a significant advancement in the minimally invasive treatment of pancreatic tumors. It offers a viable alternative for patients who are poor candidates for surgery or refusing major surgery, with growing evidence supporting its safety and efficacy in various pancreatic neoplasms, particularly in the management of PNETs and PCLs. Recent developments in device technology, procedural techniques, and adjunctive therapies have significantly broadened its clinical application. To optimize outcomes, future efforts should focus on procedural standardization, robust long-term clinical trials, integration with systemic therapies, and enhanced imaging guidance through AI. Moreover, real-world cost-benefit analyses and patient-centered outcomes are needed to refine its role in practice. As the field evolves, EUS-RFA may become a cornerstone in the multidisciplinary management of pancreatic tumors.

FOOTNOTES

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MINIREVIEWS

Utility of splenic transient elastography in assessing the presence of portal hypertension: A review

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Abstract

Portal hypertension (PH) is a major complication of chronic liver disease, often leading to serious clinical consequences such as variceal bleeding, ascites, and splenomegaly. The current gold standard for PH diagnosis, namely, hepatic venous pressure gradient measurement, is invasive and not widely available. Transient elastography has emerged as a non-invasive alternative for assessing liver stiffness (LS), and recent studies have highlighted the potential role of splenic stiffness (SS) in evaluating PH severity. This narrative review summarizes the available evidence on the utility of splenic transient elastography in assessing PH. We evaluated its diagnostic accuracy, technical challenges, and clinical applications, particularly in distinguishing between cirrhotic PH (CPH) and non-cirrhotic PH (NCPH). A comprehensive literature search was conducted using the PubMed database, focusing on studies that assess splenic elastography in the diagnosis and prognosis of PH. This review compares splenic elastography with other non-invasive imaging modalities, including MR elastography and shear-wave elastography. Additionally, we examined the role of SS using elastography in predicting the presence of esophageal varices and its potential impact on reducing the need for endoscopic screening. Studies have demonstrated that splenic elastography correlates well with PH severity, with cut-off values ranging between 45 kPa and 50 kPa for significant PH detection. Splenic elastography, when combined with platelet count and LS measurements, improves diagnostic accuracy and risk stratification for the occurrence of variceal bleeding. Despite its clinical promise, technical challenges such as patient positioning, body habitus, and probe selection remain key limitations. Notably, splenic elastography may be particularly useful in diagnosing NCPH, where LS remains normal but PH is

present. Splenic transient elastography is a valuable adjunct in the non-invasive assessment of PH. Its ability to predict varices, differentiate between CPH and NCPH, and reduce unnecessary endoscopies suggests that it should be incorporated into routine hepatology practice. Future research should focus on refining SS cut-offs, evaluating its cost-effectiveness, and integrating splenic elastography into clinical guidelines for PH management.

Key Words: Portal hypertension; Transient elastography; Splenic stiffness; Cirrhosis; Non-cirrhotic portal hypertension; Gastroesophageal varices; Liver fibrosis

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Core Tip: Splenic transient elastography is a valuable adjunct in the non-invasive assessment of portal hypertension. Its ability to predict varices, differentiate between cirrhotic and non-cirrhotic portal hypertension, and reduce unnecessary endoscopies suggests it should be incorporated into routine hepatology practice.

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INTRODUCTION

Portal hypertension (PH) is broadly defined as the clinical manifestation of elevated pressure within the portal venous system[1]. It is most commonly caused by liver cirrhosis, which may result from various underlying conditions such as viral hepatitis or metabolic dysfunction-associated steatotic liver disease[2]. However, PH is not limited to cirrhosis and can also occur in a range of non-cirrhotic conditions[3].

Evaluation of PH involves a combination of clinical history and ancillary diagnostic tools, including laboratory investigations and imaging studies. Clinical signs may include esophageal or gastric varices, palpable splenomegaly, ascites, portosystemic shunting (*e.g.*, caput medusae), and hepatic encephalopathy[4]. Laboratory findings often include a serum-ascites albumin gradient > 1.1 g/dL - calculated by subtracting ascitic albumin from serum albumin - in addition to thrombocytopenia and mild leukopenia[5]. On imaging, PH may be suggested by features such as splenorenal or other portosystemic shunts, splenomegaly, dilated portomesenteric veins, and biphasic or reversed portal venous flow on Doppler ultrasound[6].

The causes of PH are diverse and are typically classified according to their anatomical relationship to the hepatic sinusoids - the microvascular spaces where nutrient-rich blood from the portal vein is processed by hepatocytes before draining into the hepatic veins[7]. An overview of these causes is presented in Figure 1. As noted, cirrhosis remains the most common etiology of PH.

PH is typically diagnosed through a combination of laboratory testing, endoscopic evaluation for varices, and imaging studies[8]. The gold standard for diagnosing PH is the invasive measurement of the hepatic venous pressure gradient (HVPG)[9]. This procedure involves inserting a catheter with a balloon tip *via* the internal jugular vein into the hepatic vein branches. The free hepatic venous pressure (FHVP) is measured without balloon inflation, followed by the wedged HVP (WHVP) with the balloon inflated. Then the HVPG is calculated as the difference between WHVP and FHVP, expressed in mmHg.

HVPG values[10] carry important prognostic implications: > 10 mmHg indicates clinically significant PH (CSPH); > 12 mmHg is associated with an increased risk of variceal rupture; > 16 mmHg correlates with higher mortality risk.

Despite its diagnostic accuracy, HVPG measurement has notable limitations. For instance, normal or only slightly elevated HVPG values may be observed in cases of pre-hepatic or post-hepatic PH, such as in splenomegaly-related PH or cardiac-related PH[10]. Furthermore, as an invasive procedure, HVPG carries risks including bleeding and other catheter-related complications[11]. Given these drawbacks, a multimodal approach combining clinical findings, laboratory values, imaging, and non-invasive measurements is often essential for accurate diagnosis.

Transient elastography (TE), which assesses liver stiffness (LS) in kilopascals (kPa), has become a widely used tool in the evaluation of liver fibrosis and cirrhosis. Its adoption has significantly impacted hepatology by reducing the need for liver biopsy in patients with chronic liver disease[12]. Moreover, recent guidelines recommend incorporating TE-derived LS values and platelet count in patients with known cirrhosis to help avoid screening endoscopy for esophageal varices [13]. In addition, the role of spleen stiffness (SS) has gained attention in these same guidelines, where lower SS values may be used to rule out the need for endoscopic screening. However, this recommendation is currently limited to specific etiologies, primarily viral hepatitis, and is not yet generalized to all causes of PH related to cirrhosis[13].

Given the relatively recent application of TE to spleen stiffness measurement, the aim of this review was to explore the available literature on SS, including the technical limitations of using equipment initially developed for LS estimation. We evaluated current data regarding the diagnostic performance of SS (sensitivity and specificity) for identifying complications of PH - particularly the presence of varices - across different liver disease etiologies. These findings were compared

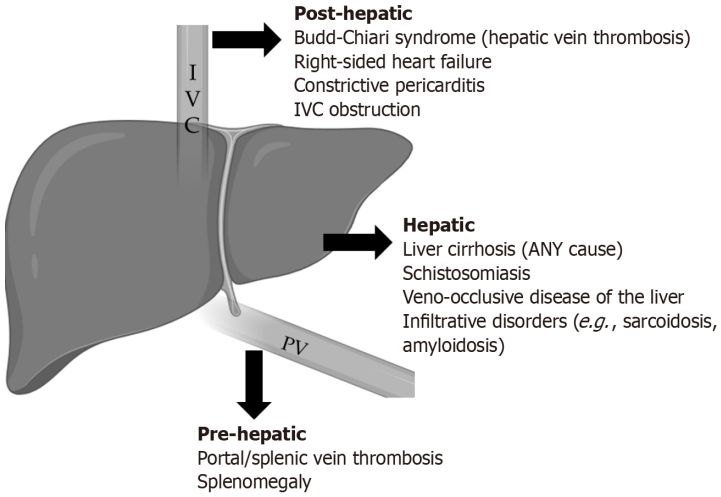


Figure 1 Some causes of portal hypertension. IVC: Inferior vena cava; PV: Portal vein. Image created using Biorender.

to existing guideline recommendations. We also examined the added diagnostic value of SS in distinguishing non-cirrhotic PH (NCPH) from cirrhotic PH (CPH). Finally, we highlighted potential areas for future research and advancement in the field. All included studies were identified through a literature search on the PubMed database. The review was conducted in a narrative format, with the goal of providing practical, clinically relevant insights for hepatologists managing patients with PH.

SPLEEN STIFFNESS – TECHNIQUES AND CHALLENGES

Several methods are available for measuring SS, of which the three most common are transient elastography, MR elastography, and shear-wave elastography. The differences between each of the methods are summarized in Table 1[14].

Despite the growing interest in SS as a non-invasive tool for evaluating PH, the optimal diagnostic cut-off remains controversial, largely due to differences in elastography modalities, study populations, and target outcomes. For instance, TE studies have proposed thresholds ranging from 26.5 kPa to 60 kPa[15] to detect significant PH, not considering the cut-off proposed by the Baveno VII guidelines at about > 50 kPa. In contrast, shear-wave elastography studies have reported lower thresholds, often between 12 kPa and 20 kPa[16], whereas magnetic resonance elastography (MRE) is associated with PH at values of about 10 kPa[17]. These discrepancies stem from differences in technical parameters (*e.g.*, probe frequency, acquisition depth), measurement protocols, and the fact that SS is not yet fully standardized across platforms.

The latest Baveno VII guidelines[13] suggest the usage of TE for the purpose of SS measurements, which is the method we concentrate on here. However, the location and size of the spleen in the left-upper quadrant make such measurements difficult and somewhat limited in certain settings[18]. For instance, in early PH, the spleen may not be sufficiently enlarged to allow acoustic capture through the relevant intercostal space. While SS *via* TE is a promising non-invasive tool, several technical factors can affect its accuracy and feasibility. Obesity, for instance, precludes accurate measurements of SS, with some studies[19] demonstrating that already at a body mass index (BMI) > 24 kg/m^3 the failure rates increase due to poor acoustic wave propagation and signal attenuation. In addition to this, the presence of ascites dampens the wave transmission interfering with the method´s accuracy[19]. In addition, spleen size smaller than roughly 93 mm[19] also hinders accurate measurements of SS.

Despite these disadvantages, reproducibility of SS measurements can be considered moderately high, with correlation coefficients ranging from 0.73 to 0.90 in different studies[20,21]. Simple maneuvers, such as telling patients to alternately inhale/exhale and hold their breath to see when the spleen is nearest to the intercostal spaces, may aid in allowing the spleen to be captured with the probe. Another maneuver is to place the patient in right lateral decubitus position such that the spleen is more prominent in its position in the left upper quadrant, having the effect of gravity pulling the spleen anteriorly, thus making it easier to get the spleen in the right acoustic window[22]. Furthermore, the use of an XL-probe may allow for easier acquisition of SS values especially in obese patients[23]. This may, however, lead to the underestimation of the actual SS with the XL-probe as compared to the M-probe, and a higher degree of uncertainty (expressed as interquartile range, IQR%) in the measurements obtained[24]. Lastly, the usage of a higher frequency (100 Hz) probe, compared to the standard "liver" probe (50 Hz), may also increase the accuracy of performed measurements and allow for higher (up to 100 kPa) values to be obtained for SS[25].

Table 1 Summary of different methods for estimation of splenic stiffness

Modality	Feasibility	Availability	Cost	Operator dependence
Transient elastography	High	Widely available	Low	High
Shear-wave elastography	Moderate	Moderately available	Moderate	Moderate
Magnetic resonance elastography	Low	Limited to tertiary centers	High	Low

Table 2 Survey of studies where splenic stiffness estimation using transient elastography for the presence of varices was performed [27-36]

Ref.	Pathologies studied	Cut-off (in kPa)	Sensitivity	Specificity
Stefanescu *et al*[27], 2011	HCV/ALD	46.4	83.5	71.0
Colecchia *et al*[28], 2012	HCV	55.0	96.0	85.0
Sharma *et al*[29], 2013	ALD/HBV/HCV/CLD	40.8	94.0	76.0
Calvaruso *et al*[30], 2013	HCV	50.0	65.0	61.0
Fraquelli *et al*[31], 2014	HBV/HCV/MPD	48.0	100	60.0
Zykus *et al*[32], 2015	ALD/HCV/CLD	50.7	78.1	77.1
Rewisha *et al*[33], 2016	HCV	43.2	92.9	84.5
Tseng *et al*[34], 2018	HBV/HCV/AIH/PBC/NAFLD/CLD	48.9	76.0	100
Ferreira-Silva *et al*[35], 2023	ALD	54.0	72.2	60.9
Lantinga *et al*[36], 2023	ALD/NAFLD/HCV/HBV/AIH	46.4	82.0	80.0

AIH: Autoimmune hepatitis; ALD: Alcoholic liver disease; CLD: Cryptogenic liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MPD: Myeloproliferative disorder; NAFLD: Non-alcoholic fatty liver disease; PBC: Primary biliary cholangitis.

SPLEEN STIFFNESS-ASSOCIATION WITH DEVELOPMENT OF VARICES

The most devastating complication of PH is the formation of bleeding esophageal varices, which carry an estimated 6-week mortality of approximately 20% following a single bleeding episode[26]. The current Baveno VII consensus guidelines recommend the use of LS and SS measurements *via* TE for the non-invasive assessment of PH. While LS cut-offs are now well established, SS thresholds remain less well-defined and are not yet universally endorsed across all etiologies, with the aforementioned guidelines mainly focusing on their use in the viral hepatitis setting[13].

As summarized in Table 2[27-36], there appears to be a reasonable level of agreement across the literature regarding SS cut-offs for identifying significant PH as suggested by the identification of varices, irrespective of the underlying PH cause. Most studies report diagnostic thresholds in the range of 45–50 kPa, consistent with Baveno VII's suggested value of > 50 kPa to rule in significant PH, although that recommendation is specific to viral etiologies. Reported sensitivities and specificities across studies generally cluster around 80%, indicating acceptable diagnostic performance for detecting esophageal varices.

Importantly, combining SS measurements with platelet count appears to enhance diagnostic accuracy, with some studies reporting sensitivity and specificity approaching 90%[37]. This combined approach may further reduce the need for unnecessary screening endoscopies and allow for a more targeted use of non-selective beta-blockers, regardless of the etiology of PH.

Although some studies have reported receiver operating characteristic values, these were not consistently available due to methodological heterogeneity and varied patient populations. Therefore, to maintain coherence and comparability, this review focuses on SS cut-offs and corresponding sensitivity/specificity values, which are more immediately applicable in clinical settings. A formal meta-analysis was not performed, as it was beyond the scope of this narrative review; however, the convergence of SS thresholds within a narrow 45–50 kPa range across studies supports this interval as a practical and reproducible reference point for clinical use.

SPLEEN STIFFNESS AIDING IN PINPOINTING CAUSE OF PH

The most common cause of PH is, as previously mentioned, the presence of chronic liver disease, specifically liver cirrhosis. However, for patients from non-western countries, and especially those originating from Africa, infectious

Table 3 Summary of some main causes of non-cirrhotic portal hypertension

Group of causes	Example of specific disorders
Immunological disorders	CVID, CD, Organ transplant patients, autoimmune conditions (*e.g.*, SLE)
Infections	Bacterial intestinal infections (esp. during childhood), helminths (*e.g.*, schistosomiasis), HIV
Medications and toxins	Thiopurines, vitamin A, chemotherapeutic agents
Thrombotic and hematological conditions	Myeloproliferative syndromes; thrombophilias predisposing to MVT
Genetic disorders	Turner syndrome

CD: Crohn's disease; CVID: Common variable immunodeficiency; HIV: Human immunodeficiency virus; MVT: Mesenteric vein thrombosis; SLE: Systemic lupus erythematosus.

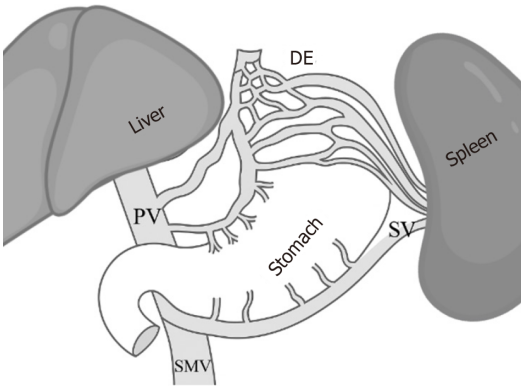


Figure 2 Portal circulation and related anatomy. The stomach's venous drainage is into the splenic vein, while the esophageal drainage (especially lower esophagus) is into the portal vein (PV), which is the reason for preferential variceal development at the lower esophagus in cirrhotic portal hypertension (PH), whereas the non-cirrhotic PH there is mainly the development of gastric varices. DE: Distal esophagus; SMV: Superior mesenteric vein; SV: Splenic vein. Image created using Biorender.

causes, such as schistosomiasis, or sequelae of prior abdominal infections, such as extrahepatic portal vein thrombosis, are the most common cause of PH, and are thus classified as NCPH[1]. Given the multitude of causes that are associated with NCPH as detailed in Table 3 below, the diagnosis may be elusive[38].

The diagnosis of NCPH should be suspected In patients presenting with signs of elevated portal pressures (*e.g.*, ascites, splenomegaly or variceal bleeds), with normal liver function tests (including prothrombin time/international normalized ratio and albumin), normal (or very slightly elevated) LS measures, and an otherwise negative work-up for liver cirrhosis (including liver biopsy). NCPH is specifically characterized, compared to CPH, by prominent splenomegaly on imaging/clinical examination alongside a relatively low LS but particularly elevated SS, when elastography is used[39]. This finding may even suggest the routine usage of SS estimations in patients with unclear PH where primary hepatic causes have been excluded.

Yet another clue for the presence of NCPH, especially when assessing for the location of varices, is the fact that there is usually a predominance of gastric varices compared to "lone" esophageal varices, which are otherwise the norm in CPH, with generally more severe thrombocytopenia[40]. The aforementioned findings are readily understandable especially when considering the venous drainage of the distal esophagus as compared to the stomach (Figure 2). This may reflect pre-portal vein causes, such as mesenteric or splenic venous pathologies; alongside the immunological/hematological basis for many of these conditions whereby the spleen is afflicted by these processes, causing increased platelet sequestration, alongside "left-sided" PH predominantly with gastric varices.

LIMITATIONS OF SPLEEN STIFFNESS IN CLINICAL PRACTICE

Despite its growing clinical utility, SS measurement *via* TE has several limitations. One key issue is its limited sensitivity in early-stage PH, where structural and hemodynamic changes in the spleen ultimately leading to splenic congestion may not yet be significant enough to elevate stiffness values[30].

Coexisting splenic pathologies, such as lymphoma, infiltrative diseases, or congestive splenomegaly from cardiac dysfunction, can also independently increase SS, potentially leading to false-positive interpretations[31]. Moreover, technical challenges like obesity, ascites, and small spleen size can impair signal acquisition and measurement success[27, 28]. These issues are particularly notable in patients with BMI > 24 kg/m² or spleens measuring < 93 mm in length[18]. While operator training and the use of XL-probes can help mitigate some of these difficulties, inter- and intra-observer

variability remains a consideration, even with standardized protocols[23]. Notably, as mentioned earlier, SS may be elevated while LS remains normal - a valuable diagnostic clue rather than a confounder[39]. This differential pattern may aid in distinguishing NCPH from CPH when integrated with clinical and laboratory findings[41].

Together, these limitations emphasize the importance of interpreting SS values in the broader context of clinical presentation, LS, platelet count, and suspected disease etiology[42,43].

FUTURE RESEARCH PERSPECTIVES

There are several promising areas for future research where the application of splenic TE could provide significant clinical value. Given the simplicity and non-invasive nature of TE for assessing both LS and SS, its broader use in patients with newly diagnosed cirrhosis and PH, regardless of underlying etiology, may offer important insights into prognosis, particularly in predicting the development of esophageal varices. The combined assessment of LS and SS, especially when interpreted alongside platelet count, may further refine risk stratification and reduce the overuse of non-selective beta-blockers. In fact, this approach may support de-prescription of beta-blockers in patients with consistently low LS and SS values, minimizing unnecessary treatment in low-risk individuals.

Another area of growing interest is the use of LS and SS in patients with NCPH, or idiopathic PH. In this setting, TE could assist both surveillance strategies and therapeutic decisions, including beta-blocker use, particularly when variceal risk remains uncertain. Finally, establishing age-specific reference values for SS represents an important research need. Normative data from healthy individuals across different age groups would enhance the interpretability of SS values in clinical practice and ensure more individualized decision-making.

CONCLUSION

In conclusion, SS measurement using TE appears to be a valuable adjunct in the evaluation of significant PH regardless of the underlying etiology. While the Baveno VII consensus limits the > 50 kPa SS threshold to patients with viral hepatitis, our review demonstrates consistent diagnostic performance across a broader range of liver diseases, supporting its potential wider applicability. When used alongside LS, SS may enhance diagnostic accuracy and reduce the need for unnecessary endoscopic evaluations in patients with newly diagnosed cirrhosis. Clinically, a combination of high LS and high SS supports CPH, whereas low LS combined with elevated SS in the appropriate clinical setting may suggest NCPH, in which SS measurement may aid diagnostic confirmation. Further research is warranted to define SS's role in beta-blocker de-prescription and to support its integration into general clinical guidelines for PH management.

FOOTNOTES

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MINIREVIEWS

Future of inflammatory bowel disease treatment: A review of novel treatments beyond guidelines

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Abstract

Inflammatory bowel disease (IBD) is a chronic condition consisting of two main types: Crohn's disease and ulcerative colitis. Conventional treatments for these diseases include aminosalicylates, corticosteroids, immunomodulators, and biologics. However, these treatments have several drawbacks, including high costs for patients and numerous side effects. Recently, advanced treatments have been developed, such as small-molecule therapies, targeted biologics, innovative drug delivery systems, and microbiome-based interventions. Emerging therapies like anti-interleukin-23 monoclonal antibody inhibitors, sphingosine-1-phosphate receptor modulators, and Janus kinase inhibitors are more specialized in reducing immune activity. They enhance bioavailability, reduce side effects, and specifically target the gastrointestinal tract without affecting other systems. Innovative drug delivery systems for IBD, such as nanoparticles, hydrogels, and microgrippers, improve bioavailability and prolong drug release. The combination of conventional and advanced therapies may benefit from the synergistic effects of both. Furthermore, fecal microbiota transplantation and probiotics can help restore the balance of gastrointestinal microbiota, reducing disease flare-ups. Advances in artificial intelligence, endoscopic techniques, and stem cell therapies have shown great potential in treating IBD, although several significant challenges remain. Treating this disease requires multidisciplinary integration and the application of technology and telemedicine.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Biological treatment; Microbiome; Probiotics; Fecal microbiota transplantation; Innovative drug

delivery systems; Endoscopy

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Core Tip: Inflammatory bowel disease is a chronic gastrointestinal disorder causing persistent inflammation. Traditional treatments include aminosalicylates, corticosteroids, immunomodulators, and biologics. Advanced treatments like small-molecule therapies, targeted biologics, and innovative drug delivery systems have improved bioavailability and reduced side effects. Combining conventional and advanced treatments is crucial for effective treatment.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a group of inflammatory bowel conditions characterized by chronicity and a relapsing course. The two major forms are Crohn's disease (CD) and ulcerative colitis (UC). Generally, IBD is a multifactorial disease influenced by genetic factors, environmental factors, mucosal barrier dysfunction, disturbances in the gastrointestinal microbiota, dysregulated immune responses, and lifestyle factors[1,2]. Due to their chronic nature, these diseases affect patients' quality of life and require lifelong care. Up to 75% of patients with CD and 30% with UC may require surgery. The incidence of IBD has increased over time in Egypt. The early twenty-first century has shown a rapidly increasing occurrence in newly industrialized countries; for example, in China, the incidence of IBD was about 1.74 per 100000 people. Although morbidity remains substantial in western countries, its incidence has increased to approximately 0.3% of the population. The lifelong use of expensive medications, the relapsing nature of IBD, surgeries, and hospitalizations can impact the financial state of the healthcare system and create significant financial burdens for patients and their families[3,4].

Traditional treatment approaches include aminosalicylates, corticosteroids, immunomodulators, and biologics, along with surgical resection when necessary. Among these strategies, corticosteroids play the most vital role in inducing remission during disease flares. However, long-term use of corticosteroids is associated with risk factors such as adrenal suppression, opportunistic infections, osteoporosis, and glucose intolerance; it is generally not recommended for maintenance therapy[5].

Recent years have shown great improvement in therapeutic options for IBD; inhibitors of tumor necrosis factor have been successful as they allow for long remission periods. However, 40% of patients in clinical trials and 10%-20% of patients in clinical series stopped responding to treatment after 1 year, noted in 23%-46% of patients. Newer approaches such as small molecule inhibitors (*e.g.*, JAK inhibitors) and targeted biologics [*e.g.*, anti-integrins, anti-interleukin (IL)-12/23][6] are emerging. Other strategies for IBD treatment involve small molecules that improve intestinal microecology, a complex gut ecosystem of microbes and immune interactions important for digestion and immune stability, and cell therapies to decrease inflammation and support tissue repair. Education on the importance of diet and psychological support is also essential. Together, these treatment methods aim not only to maintain remission but also to promote healing of the gastrointestinal (GI) mucosa from inflammation and restore normal mucosal structure. In this review, we concentrate not only on standard and emerging medications but also on future therapeutic directions for IBD treatment[6-8].

CURRENT STATE OF IBD TREATMENT

Overview of IBD

IBD is primarily comprised of CD and UC. These conditions are characterized by persistent inflammation of the gastrointestinal tract, significantly affecting patients' daily lives. Patients with IBD often experience abdominal pain, diarrhea, fatigue, and weight loss. If IBD progresses, it can lead to severe complications such as bowel obstructions or perforations, fistulas, and an increased risk of colorectal cancer in older patients. The symptoms and signs of IBD can vary significantly; some patients experience intermittent flare-ups, while others endure chronic disease activity that requires ongoing care[2]. The causes of IBD remain elusive, possibly due to a complex interaction of genetic predisposition, environmental factors, immune dysfunction, and changes in intestinal microbiota. Recent epidemiological data suggests a concerning increase in IBD cases in newly industrialized nations, likely reflecting changes in dietary habits and environmental exposures[6].

While the incidence appears to have stabilized in highly developed regions, IBD continues to impose a significant burden on healthcare systems worldwide. Managing IBD has historically involved the use of medications like aminosali-

cylates and corticosteroids to address signs and symptoms. Nevertheless, there has been a remarkable shift towards utilizing biologics that target inflammatory pathways. Biologics, including anti-tumor necrosis factor (anti-TNF), have emerged as essential treatments for mild to severe cases. Biologics have a high capacity to improve remission and control disease progression[7].

Despite recent developments in treatment options, including small molecules targeting various inflammatory pathways, many patients still experience treatment failures or reduced responses over time. This highlights the urgent need for ongoing research into both established treatment options and innovative methods to enhance treatment effectiveness. As healthcare providers develop personalized therapy plans based on factors like disease severity and specific complications, attention has shifted toward achieving mucosal healing. This new approach marks significant progress in how clinicians assess the success of treating IBD[7,8].

Standard treatments

IBD has substantially evolved, with a broad range of pharmacological treatments that aim to decrease symptoms and induce and maintain remission. Common treatment plans include corticosteroids, biologics, and immunomodulators. During flare-ups, corticosteroids are the most commonly used because they help to suppress the immune response and decrease inflammation. Drugs like prednisone and budesonide can effectively alleviate symptoms within days; however, long-term use may result in significant risks such as osteoporosis, high blood pressure, increased susceptibility to infections, adrenal suppression, and glucose intolerance[2,6].

Moreover, the management of IBD biologics has changed by using targeted inflammatory pathways. Anti-TNF agents, such as infliximab and adalimumab, have been crucial in achieving remission for many patients with mild to severe IBD. Infliximab is administered through intravenous infusion with an initial loading dose, followed by infusions every few months. In contrast, adalimumab offers a subcutaneous option that may potentially improve patient compliance due to its simpler administration. While these biologics are generally well tolerated, they carry a higher risk of infections due to their immunosuppressive effect. However, these infections are manageable in clinical practice. Furthermore, some patients also demonstrate a loss of response to treatment over time, primarily due to immunogenicity, which can lead to the development of anti-drug antibodies[7].

Immunomodulators like azathioprine and mercaptopurine play an essential role in maintaining remission after corticosteroid treatment or the initiation of biologics, as these tablets inhibit the increase of immune cells. These capsules help reduce dependence on corticosteroids and help sustain remission over prolonged intervals; however, careful monitoring is vital due to potential side effects, including liver toxicity and bone marrow suppression[8].

Limitations of current treatments

Therapies for IBD face significant challenges for their effectiveness. While biologics and small-molecule treatments have revolutionized IBD control, many patients do not benefit from initial treatment. Furthermore, secondary loss of response is common, as almost half of the patients who initially respond to biologics eventually experience treatment failure over time, complicating long-term management[7-9]. Current therapeutic drugs also have serious adverse effects. Corticosteroids, once a staple in IBD therapy, can lead to complications such as osteoporosis, diabetes, and weight gain[2]. Immunosuppressants, including methotrexate and azathioprine, increase the risk of liver toxicity and enhance susceptibility to infections. Biologics, primarily anti-TNF agents, can also cause immunogenicity, leading to reduced effectiveness or hypersensitivity reactions[8].

Success rates for these therapies are often disappointing, with clinical remission rates ranging from 30% to 50%. Only approximately 40% of patients maintain remission for a year after starting biologic treatment. Mucosal restoration is a treatment objective; however, histological examinations remain underutilized due to complexities and standardization issues. The situation is further complicated by the lack of therapeutic agents that specifically target IBD. Patients who do not respond to first-line treatments often experience a shortage of alternatives, worsened by the exclusion of refractory patients from medical trials[7-9]. Moreover, the high costs of biological medications create financial burdens on healthcare systems and limit patient access. Therefore, despite advances in IBD management, ongoing studies are crucial for developing modern treatment strategies with greater efficacy and safety[10,11] (Table 1).

EMERGING THERAPIES FOR IBD

Small molecule therapies

New therapies for IBD have focused on directing pathways related to inflammation. Traditional treatments depend on immunosuppressive agents, but biologics and small molecules have emerged as refined alternatives. Tumor necrosis factor inhibitors demonstrate this shift by neutralizing TNF- alpha, a key cytokine in gut inflammation. However, patient responses vary, highlighting the need for alternative strategies[12]. Advanced treatments aim to delay various cytokines and signaling pathways. JAK inhibitors like upadacitinib and filgotinib block intracellular signaling cascades stimulated by cytokines such as IL-6 and IL-23, reducing inflammation in IBD patients. Sphingosine- 1- phosphate receptor modulators prevent lymphocyte migration, further decreasing the GI inflammatory response[13,14] (Table 1). Ozanimod was the first Food and Drug Administration - approved modulator for UC in May 2021. It modifies lymphocyte distribution and diminishes intestinal inflammation by limiting lymphocytes to lymphoid tissues and restricting their movement to inflamed gut areas. Clinical studies highlight ozanimod's efficacy in inducing remission for those with moderately to severely active UC[13]. Moreover, anti-IL-23 monoclonal antibodies such as mirikizumab target specific proteins involved in inflammation, demonstrating favorable safety profiles while alleviating IBD symptoms[15].

Table 1 Distinction between biologics *vs* small molecules in inflammatory bowel disease

Feature	Biologics	Small molecules
Route of administration	IV-Subcutaneous	Oral
Risk of immunogenicity	High	Low
Onset of action	Moderate to slow	Fast
Long-term safety	Documented	Low data
Cost	Variable	High
Combination use	Immunomodulators	Biologics (some)

Innovative anti- integrin drugs like etrolizumab focus on the α4β7 integrin pathway. They display effectiveness in mucosal healing for UC. CCR9 antagonists work by blocking T- cell migration to the gut, which is particularly beneficial for Crohn's patients. These trends provide a dynamic view of IBD control, opening new avenues for improving patient outcomes. New biologics target specific interleukins and immune mediators involved in IBD pathogenesis. By concentrating on integrins that facilitate leukocyte adhesion, these treatment plans decrease inflammatory cellular infiltration into the gut. This focused approach limits systemic adverse outcomes associated with traditional immunosuppressive treatments and improves therapeutic results, allowing clinicians to effectively manage patients' disease characteristics [16]. Recent medical investigations have shown promising effects for various progressive treatments of IBD. JAK inhibitors like upadacitinib and filgotinib have demonstrated significant effectiveness in mild to severe UC by focusing on the JAK-STAT signaling pathway. Mirikizumab and guselkumab have achieved high remission rates exceeding 50%. Selective IL-23 inhibitors have provided strong protection and efficacy in patients who were unresponsive to other biologics[15]. Studies like VARSITY indicated that vedolizumab can be more powerful than adalimumab in achieving remission[17,18]. Researchers are exploring combination strategies, including biologics with small-molecule capsules, to optimize treatment responses[19]. New agents such as sphingosine-1-phosphate receptor modulators are being investigated for their mechanisms to effectively control IBD[20-23].

TARGETED BIOLOGICS BEYOND CURRENT STANDARDS

Development of novel biologics

These agents can be categorized into groups, including anti-TNF therapies that block tumor necrosis factor-alpha and anti-integrin therapies that prevent leukocytes from infiltrating the gut. Innovative biologics targeting interleukins, especially IL-12 and IL-23, are showing favorable results in managing both CD and UC.

Several clinical trials highlight the value of these new agents. The UNITI-1 and UNITI-2 trials examined the anti-IL-12/23 monoclonal antibody ustekinumab used for patients with CD who had previously failed treatment attempts with anti-TNF therapies. The study shows response rates of 34.3% and 33.7% with ustekinumab compared to 21.5% with placebo at week 6. UNITI-2 involved biologic-naïve patients, with significantly higher response rates of 51.7% and 55.5% in the ustekinumab group compared to 28.7% in the placebo group[18].

Vedolizumab is a monoclonal antibody that suppresses α4β7 integrin, and it was tested in the GEMINI 1 and GEMINI 2 trials. At week 6, 47% of patients with UC (GEMINI 1) showed a clinical response; in contrast, 25% in the placebo group exhibited a clinical response. Vedolizumab demonstrated major efficacy in both inducing and maintaining remission in CD (GEMINI 2)[19,20].

A comparison between ustekinumab and adalimumab in patients with moderate-to-severe CD was recently illustrated in the SEAVUE trial. At week 52, 65% of patients on ustekinumab and 61% on adalimumab achieved clinical remission. Remarkably, ustekinumab was associated with a decreased rate of treatment discontinuation (15% *vs* 24%) and fewer serious adverse effects, supporting its positive risk-benefit profile[21] (Table 2).

Recently, Janus kinase inhibitor medications have offered an alternative option for patients who have not achieved adequate results or experienced significant side effects with traditional biologic treatments. Nevertheless, challenges remain, such as the so-called "ceiling effect", which suggests that monotherapies may not provide sufficient clinical improvement for all patients[12]. This situation has generated interest in combination therapies that integrate various biologics or small molecules. Ongoing research focuses on enhancing these treatment strategies by improving medical approaches that consider individual patient profiles, aiming to refine predictions for therapeutic responses and to enhance safety, along with continuous investigation into biomarkers and genetic variations associated with IBD[13,16].

Safety profiles and effectiveness in different IBD subtypes

The effectiveness of biologics can vary widely among different patient groups depending on many factors, such as the type of disease, whether it is CD or UC. Additionally, effectiveness and safety may be influenced by a patient's genetics, medical and family history, compliance, and response to treatment. Clinical studies indicate that approximately 13%-46% of individuals with IBD do not respond to biologic therapies or experience a diminishing effect shortly after beginning treatment. This lack of response is often associated with the unique interactions of the immune system, where some

Table 2 Summary of clinical trials in inflammatory bowel disease treatment[17,18,21]

Trial name	Intervention	Disease	Ref.
UNITI 1-2	Ustekinumab	Crohn's disease	
GEMINI 1-2	Vedolizumab	UC/Crohn's	[19,20]
SEAVUE	Ustekinumab *vs* Adalimumab	Moderate-severe Crohn's	
VARSITY	Vedolizumab *vs* Adalimumab	UC	

UC: Ulcerative colitis.

patients activate alternative inflammatory pathways that circumvent cytokine suppression. For instance, biomarkers such as fecal calprotectin have demonstrated potential in predicting treatment responses; higher levels are typically linked to an lack of effectiveness from therapies like Infliximab, while reduced levels following the initiation of Vedolizumab can indicate a positive response[24,25]. Anti-TNF agents (*e.g.*, infliximab, adalimumab) are associated with an enhanced risk of infection, including tuberculosis and fungal infections, due to immunosuppression. Moreover, these drugs may increase the risk of lymphoma. One important limitation of these drugs is immunogenicity, as patients can develop antibodies against the drug, causing loss of response. Vedolizumab has selectivity for the gut, minimizing systemic adverse reactions and immunosuppression. Clinical trials have demonstrated a positive safety profile with a minor risk of systemic infections. Ustekinumab targets the IL-12 and IL-23 pathways and has demonstrated a decreased rate of serious adverse reactions in the UNITI-1 and UNITI-2 trials[18]. Upper respiratory tract infections and headaches are common side effects of this drug. Moreover, its immunogenicity is lower than anti-TNF therapies[14].

New agents focused on distinct inflammatory pathways are beginning to emerge, but their efficacy and safety require thorough assessment across various IBD populations to develop tailored treatment strategies that address these differences.

MICROBIOME-BASED THERAPIES

Role of the gut microbiome in IBD

The colonic lumen boasts the highest bacterial count within the human body, harboring about 10^{11} to 10^{14} bacteria, predominantly gram-positive and gram-negative species. This is followed by the oral cavity, ileum, jejunum, and duodenum, respectively. Each individual possesses a diverse range of intestinal species, ranging from 100 to 150, which provide crucial functions, including digesting fiber, producing nutrients, activating immune responses, and preventing pathogen colonization. However, individuals with IBD have a decreased bacterial range, increased fungi and bacteriophages, and a disruption of the enteric microbiota's composition and function. This microbial imbalance, called dysbiosis, has been identified in the intestines of IBD patients. While similar studies are essential, alterations have also been observed in both CD and UC patients[26].

Experimental studies have provided evidence supporting the link between dysbiosis and intestinal inflammation. For instance, the role of CD-associated adherent-invasive *Escherichia coli* in causing chronic experimental colitis and the induction of experimental colitis with a high Th1 response through *Klebsiella pneumoniae* from a CD-affected individual have been demonstrated. Additionally, *Fusobacterium varium* traces from UC patients can invade epithelial cells compared to strains from other patients. Certain *Clostridium* species and *Fusobacterium prausnitzii* are considered anti-inflammatory microbes. *Clostridia*, the dominant intestinal microbes, produce short-chain fatty acids (SCFAs) and lead to the generation of colonic regulatory T cells or IL-10-producing B cells and macrophages. These cells help protect against experimental colitis by reducing the abundance of *Enterobacteriaceae*. *Fusobacterium prausnitzii*, another prominent SCFA producer, can induce IL-10 production in both human and murine dendritic cells[27].

Emerging research indicates that restoring a balanced microbiome may offer a promising therapeutic method for managing IBD. Interventions like fecal microbiota transplantation (FMT) have demonstrated effectiveness by addressing dysbiosis. Probiotics can help restore beneficial intestinal flora, while prebiotics provide essential nutrients that are vital for these helpful microbes to thrive. Furthermore, modern techniques are being developed alongside engineered probiotics and advanced treatment options such as phage therapy, which aim to combat harmful microorganisms present in the intestine[28].

Probiotics, prebiotics, and FMT

Probiotics, prebiotics, and FMT are modern techniques for managing IBD. Probiotics are live microorganisms introduced into the body to restore beneficial gut flora. Well-regarded strains like Bifidobacterium and Lactobacillus have received recognition, while newer strains like *Faecalibacterium prausnitzii* are emerging with promising scientific validations. These probiotics can modulate inflammatory responses and re-establish mucosal barrier integrity, which is essential for people with IBD[26].

Prebiotics, non-digestible components in fine meals, play a vital role in supporting beneficial microorganisms. They help maintain microbial stability by serving as food sources for probiotics and encouraging a diverse gut microbiome.

Research shows that certain fibers and starches can affect gut flora. FMT involves transferring stool from a donor to restore microbial diversity in patients with IBD-associated dysbiosis. Clinical studies have validated that FMT can induce remission in individuals with UC and CD; however, variations in donor microbiota can influence treatment outcomes. Therefore, careful screening of donors is essential due to safety concerns related to the potential transmission of pathogens[26-28].

Studies have identified microbial profiles associated with distinct IBD forms, suggesting that personalized treatment based on male or female microbiomes can be beneficial. For example, a decrease in specific bacteria like *bifidobacteria* during CD flare-ups underscores the need for tailored interventions. Improvements in metagenomics and metabolism are supporting this personalized approach by clarifying the connections between diet, microbial products, and immune functions. Consequently, future therapies are expected to integrate microbiota analysis into routine clinical practice, enhancing treatment expectations and patient outcomes. Furthermore, next-generation probiotics and microbe-based treatments are being explored as adjuncts to traditional therapies, potentially improving efficacy while minimizing adverse reactions[28].

PERSONALIZED MEDICINE APPROACHES

Biomarker-driven treatment strategies and genetic profiling

Biomarker-driven strategies for treating IBD depend on affected person characteristics to anticipate therapy responses and refine treatment selection. Key immune markers, such as fecal calprotectin and lactoferrin, indicate active intestinal inflammation and long-term treatment efficacy. High fecal calprotectin levels suggest inadequate therapeutic response in patients with severe UC treated with Infliximab, while lower levels of calprotectin may also indicate effective mucosal healing and clinical improvements with medications like Vedolizumab[24].

Genetic profiling also shows variations in responses to biologic treatments, guiding treatment alternatives. TPMT genotyping is indicative of the safety of thiopurine therapy (*e.g.*, azathioprine, 6-mercaptopurine). TPMT enzyme activity differs depending on genetic polymorphisms that affect drug metabolism; the European Crohn's and Colitis Organisation recommends routine TPMT testing before starting thiopurine use. When TPMT activity is normal, standard dosing is safe. Intermediate activity suggests that the patient requires dose reduction due to the risk of myelosuppression. When TPMT enzyme activity is low or absent, the patient is at high risk of toxicity and thiopurines should be avoided[5]. Improvements in technology have generated useful resources for the identification of precise biomarkers linked with responses to distinctive treatment options, allowing the development of personalized treatment strategy that improve efficacy and reduce issue outcomes. Furthermore, continuing studies into the contribution of microbial family members to IBD suggests the ability to contain microbiome analyses into biomarker frameworks. This method may improve patient classification and generate useful healthcare resources to choose strong combination treatment strategy or establish new treatments based on precise biomarker profiles[5,25].

COMBINATION THERAPIES

Rationale for combining therapies

Combination therapy for IBD is gaining acceptance as a powerful method that benefits from the synergistic effects of multiple agents. Traditionally, combining biologics with immunomodulators has proven more effective, primarily in achieving remission for conditions like CD and UC. This approach enhances therapeutic benefits and reduces immunogenicity concerns, thereby prolonging the effectiveness of biologics[1]. As drug development progresses, dual-targeted treatment options emerge to simultaneously address multiple IBD pathways. This comprehensive strategy offers more efficient symptom management and remission. Combining newer biologics with small-molecule drugs or established treatments may also provide advancements for complex IBD cases. Initial studies show promising results, but safety and long-term outcomes remain significant concerns. Increased risk of infection and malignancy necessitate careful patient selection based on gender, age, and pre-existing health conditions[29,30].

Clinical trial evidence supporting combination approaches

Combination therapy has demonstrated greater efficacy compared to monotherapy with infliximab and azathioprine. Azathioprine enhances infliximab bioavailability and prevents antibody development. The United Kingdom personalized anti-TNF therapy in CD study indicated higher remission rates in patients receiving concomitant immunosuppressive therapy, irrespective of drug concentration or antibody development. Advanced combination treatment, involving the use of two or more advanced therapies (biological agents and/or oral small molecules), is currently being investigated for refractory IBD, high-risk phenotypes, and extraintestinal manifestations[27,29]. The most common biological combinations include vedolizumab and ustekinumab or vedolizumab and anti-TNF. Tofacitinib is the most commonly evaluated combination with oral small molecule drugs, including vedolizumab or ustekinumab[29]. However, the evidence supporting advanced combination therapy primarily comes from uncontrolled retrospective case series and cohort studies involving highly refractory patients, raising questions about safety and efficacy. The first randomized controlled trial evaluating dual biological therapy in 2007 focused on the safety and tolerability of infliximab and natalizumab rather than efficacy. The VEGA study was a phase 2 induction trial evaluating the use of guselkumab and golimumab in patients with UC[31]. Dual-biologic therapy is also gaining traction, with trials studying combinations like vedolizumab

and ustekinumab for refractory IBD. While promising results have been reported in studies like the EXPLORER trial that assessed a three-drug regimen, many of these trials have limited scope, raising questions about their generalizability across different populations[29]. Further research is needed to evaluate the long-term safety of combination strategies for managing IBD. Initial findings suggest tolerability and efficacy for specific subgroups, but larger trials are necessary to verify their applicability.

INNOVATIVE DELIVERY METHODS

Overview of novel drug delivery systems

Recently, innovative drug delivery systems (DDS) have developed transformative solutions in the treatment of IBD, significantly enhancing healing effectiveness while reducing side effects. These systems aim to deliver medications directly to the inflamed areas within the intestine. Advancements in these fields involve nanoparticles, as these particles can protect drugs from degradation and ensure their release at specific locations by encapsulating them. In addition to improving bioavailability, nanoparticles allow for lower doses, thereby decreasing the risk of adverse reactions[32]. Nanoparticle-based DDS can be designed in different forms, including lipid-based nanoparticles (*e.g.*, liposomes, solid lipid nanoparticles), which have the capability of carrying both hydrophilic and hydrophobic drugs. Polymeric nanoparticles, such as PLGA PEGylated systems, have an excellent capacity to control and release drugs. Inorganic nanoparticles (*e.g.*, gold, silica, magnetic) are often used with other therapeutic or diagnostic agents due to their responsiveness to external stimuli[33].

Another interesting development is the introduction of a stimuli-responsive drug delivery system that reacts to positive physiological signals, such as changes in pH. This is useful in the gastrointestinal tract, as the colon has a more neutral to alkaline pH. Therefore, it is a suitable target for pH-sensitive coatings that dissolve specifically at higher pH levels (*e.g.*, Eudragit-coated capsules), as well as temperature changes or enzymatic activity. The presence of certain enzymes, such as azoreductase and glycosidase, leads to the degradation of linkages in carriers and subsequent drug release. Redox-responsive systems release drugs through oxidation-sensitive moieties or disulfide bonds in response to high glutathione levels or reactive oxygen species found in inflammatory tissues. These enhanced structures confirm that medications are released once they reach the inflamed areas of the intestine, thus boosting treatment efficacy. For instance, hydrogels and microgrippers were designed to enhance drug transport through mechanisms that adjust release timing based entirely on the environment within the gastrointestinal tract[33]. Implantable devices provide a means for prolonged medication release over extended periods, which can address issues faced by IBD patients, such as poor adherence, flare-ups, and reduced dosing frequency. Recently, there have been collaborations between nanotechnology and personalized medicine approaches, such as biomarker-guided DDS, which allow drug release in response to the levels of gastrointestinal inflammatory markers like calprotectin and TNF-α. Moreover, ligand-functionalized nanoparticles attach to overexpressed molecules in inflamed mucosa, such as ICAM-1 or VCAM-1[33,34]. This collaboration aims to develop a treatment strategy that is personalized to each patient's characteristics, aiding in the development of patient-centered strategies that can emphasize both convenience and effectiveness. By combining innovative materials with enhanced biocompatibility and functionality, these modern techniques demonstrate the potential for improvement in safety profiles while more effectively targeting local inflammation than conventional methods. With this modern technology, including precision nano-carriers and integrated systems that combine drug delivery with real-time tracking, there is considerable potential to enhance patients' outcomes in IBD treatment[35].

Enhancements in patient compliance and drug bioavailability

Cutting-edge drug delivery systems have improved to enhance drug bioavailability and patient adherence, which is critical in the treatment of IBD. The strategy is designed to allow lower dosages without modifying effectiveness. Controlled-release mechanisms improve the pharmacokinetics of IBD drugs by significantly enhancing bioavailability and compliance by ensuring a constant delivery of medicinal drugs over prolonged intervals, thus reducing dosing frequency and improving adherence[35]. Time-controlled DDS allow for the gradual release of drugs throughout the GI tract, prolonging the duration of action. Additionally, mucoadhesive nanoparticles increase absorption by prolonging contact time with the mucosa and improving medication retention at the inflammation site. Moreover, self-emulsifying drug delivery systems and liposomes improve the solubility of poorly water-soluble drugs, leading to enhanced drug absorption and decreased dosage requirements[30-32].

One of the main challenges in chronic diseases like IBD is patient adherence, particularly when treatment involves multiple medications with different dosing schedules. Oral drug transport remains favored due to its non-invasive nature and the gastrointestinal tract's large surface area, which facilitates absorption. Once-daily oral DDS has been developed to replace multiple daily doses. Moreover, oral colon-targeted systems containing enteric-coated capsules and microbe-triggered preparations provide alternatives to injections or rectal treatments. Innovations like nanoparticles and hydrogels enhance solubility and stability across various pH levels in the GI tract. Advanced technologies such as smart drug delivery systems can assess patients' compliance and adjust doses based on physiological responses. Emerging focused methodologies increase local drug concentrations in targeted areas while decreasing systemic risks. This focused technique improves healing effectiveness and reduces adverse reactions associated with conventional treatment options [32,35].

CHALLENGES AND CONSIDERATIONS

Regulatory delays in approval of novel treatments

Regulatory challenges in the approval of modern treatment plans for IBD face significant restrictions on the acceptance of advanced drug delivery solutions. The process is often complicated and lengthy, requiring pharmaceutical companies to navigate a complex landscape of guidelines designed to ensure safety and efficacy. Firms must adhere to strict standards throughout the drug development process, which can increase manufacturing costs and prolong timelines. This issue is continuously growing alongside the continually expanding understanding of IBD's underlying mechanisms, adding further layers of complexity to regulatory submissions. Concerns about how new IBD treatment plans function may also extend review times as regulatory organizations seek comprehensive data[35].

Another essential component is the need for substantial safety data linked to modern delivery techniques, such as nanoparticles or implantable devices. The government requires extensive clinical tests that not only demonstrate effectiveness but also establish long-term safety profiles before approving new medicines. This requirement can lead to delays if primary research yields unexpected results or if additional data is difficult to address new concerns. Financial constraints also impact regulatory timelines; the high costs associated with participating in clinical trials may deter smaller groups from pursuing innovative approaches. Thus, while advanced drug delivery systems hold significant promise for enhancing treatment outcomes in IBD patients, regulatory challenges remain significant obstacles that require careful planning and prudent resource allocation[35,36].

Cost implications and healthcare accessibility

Management of IBD has significant financial effects. Because IBD is a chronic condition, it requires long-term management, healthcare visits, and careful monitoring. Collectively, these contribute to increasing healthcare costs. For example, in Western Europe, the annual costs for CD range from about €6338 to €8004, while individuals with UC incur expenses between €3600 and €4819. These figures highlight the financial burden on each patient and healthcare systems. The rising incidence of IBD exacerbates this issue by elevating demand for expensive biologic therapies and specialized medical services. The financial challenge stems not only from medications but also from hospital stays and visits. Moreover, indirect costs arise from work-related disabilities, which account for nearly 50% of the total losses associated with the disease[37-40].

Additionally, innovative DDS have been developed and improved with financial cost in mind, as these technologies aim to treat IBD with reduced drug dosage and enhanced bioavailability[32]. Combining these strategies with telemedicine, which may contribute to decreasing patient hospitalization, an extra streamlined care model can be created that better addresses patients' wishes while also relieving financial burdens. As international healthcare systems attempt to find sustainable answers in light of the increasing occurrence of IBD and its associated finances, adopting comprehensive techniques that include telemedicine may enhance accessibility without sacrificing quality of care[39,40].

Discussion of long-term safety and efficacy data

While novel drug delivery techniques in IBD aim to release medications for long-term use precisely within the gastrointestinal tract, they require extensive long-term evaluations for safety and effectiveness. Regulatory agencies demand substantial medical statistics to assess the long-term safety of nanoparticle or biologic treatments, particularly those that may evoke immunogenicity[33,34]. Long-term research monitors both efficacy and delayed side effects. Comprehensive follow-up care is vital for identifying adverse effects arising from novel formulations or delivery strategies. Innovative systems enhance bioavailability; however, they may also have distinct toxicological profiles. Changes in pharmacokinetics due to localized transport could result in unexpected interactions with existing medications or dietary elements, necessitating ongoing patient monitoring. Evaluating the impact on quality of life is paramount, considering the chronic symptoms and flare-ups experienced by IBD patients. Management techniques should prioritize long-term well-being alongside short-term clinical outcomes[38].

Present and future of endoscopy precision for IBD

Endoscopy is an important method for enhancing diagnosis accuracy and management of IBD. Traditional techniques such as white-light endoscopy are now being advanced by incorporating superior strategies that allow for sharper imaging and improved visualization of the mucosal structure. These techniques include narrow-band imaging and blue laser imaging, which provide valuable insights into inflamed and healing tissue, thereby enhancing the ability to assess disease activity. Endoscopic techniques help diagnose patients with dysplastic lesions due to chronic inflammation from IBD. Early visualization of these lesions is crucial, as the prognosis of these lesions is associated with their early detection [36]. In pediatric IBD, transabdominal and transperineal ultrasound is more effective than using endoscopy because these modalities offer gastrointestinal imaging without the need for general anesthesia. Furthermore, the introduction of unsedated transnasal endoscopy has increased access to upper gastrointestinal evaluations for young children with CD [41].

Artificial intelligence (AI)-driven algorithms are predicted to enhance diagnostic accuracy by reading endoscopic images with greater reliability than human evaluators. This technology should provide real-time insights into disease severity and help establish personalized treatment strategies based entirely on patient profiles. Additionally, advancements in endoscopic resection techniques empower gastroenterologists to promptly address dysplastic lesions within the colon. Procedures such as endoscopic mucosal resection and endoscopic submucosal dissection allow for the complete removal of lesions that present a risk for colorectal cancer, all while avoiding more invasive surgical methods. These developments highlight an evolving paradigm in which endoscopy goes beyond its traditional role as merely a

diagnostic tool, establishing itself as a crucial approach in therapeutic management and allowing healthcare professionals to deliver advanced care to individuals with IBD[42].

FUTURE DIRECTIONS IN IBD TREATMENT

Anticipated advancements in IBD research, treatment options and stem cells

Research and treatment of IBD are continuously advancing due to a deeper understanding of the disease and treatment options, focusing on developing personalized treatments that rely on each patient's unique genetic, immunological, and environmental features, aiming to improve treatment efficacy, bioavailability, and safety. New medications, such as immunomodulatory agents, immune checkpoint inhibitors, and cytokine-targeted healing therapies, target specific pathways involved in IBD, potentially improving long-term remission rates and reducing treatment failures.

Stem cells have the capability to significantly improve persistent intestinal inflammation by modulating immune cells and repairing the intestinal mucosal barrier. Although hematopoietic stem cell therapy can improve disease chronicity and maintain remission in CD, safety is a major concern due to the risks of severe immunosuppression, lethality, and graft rejection. Clinical studies using mesenchymal stem cell therapy have primarily focused on patients with perianal fistulous CD, yielding mixed outcomes. The ADMIRE-CD trial evaluated darvadstrocel, an expanded adipose-derived MSC product, for managing complex perianal fistulas in CD. The study described considerably higher rates of combined clinical and radiological remission. Relying on these results, the European Medicines Agency accepted darvadstrocel in 2018 as the first stem cell-based therapy for IBD[43,44].

The primary challenge in stem cell therapy is preserving homogeneity through uniform standards and managing comparisons within the tissue source and stem cell culture. The heterogeneity in outcomes between individuals ultimately influences the consistency of IBD clinical research. There is also hope for a standardized protocol regarding infusion mode, dosage, and time interval of stem cell therapy, along with the establishment of clear warning signs and contraindications. While stem cell treatment in IBD remains in its preclinical stages, it is regarded as a true therapy for these debilitating diseases[43].

The goal of ongoing research on non-invasive diagnostic techniques is to enhance the evaluation of disease severity while reducing the patient's discomfort. The integration of advanced diagnostic tools with healing methods is expected to shift the care of IBD from reactive to proactive, positively impacting the patient's experience through tailored interventions that address the medical and psychosocial factors of living with IBD[44].

The role of technology and telemedicine

The incorporation of technology and telemedicine into IBD management is transforming patient care, allowing for rapid intervention and consistent oversight. Moreover, AI can evaluate large datasets from electronic health information and genomic studies to improve diagnoses and individualize treatment strategies by recognizing patterns in patient responses [5]. For example, assessing mucosal healing, detecting dysplasia, and monitoring disease activity in IBD patients can be evaluated using AI-based image analysis. An AI-assisted endoscopy system is a real-world application that improves polyp exposure in real time and has potential applications in IBD surveillance colonoscopy. Big data analytics is revolutionizing care quality by enabling healthcare providers to effectively track outcomes. Nanotechnology and smart delivery systems that respond to physiological signals present directed therapy to inflamed regions, decreasing side effects and increasing drug bioavailability. Together, these emerging technologies show the potential for a more customized, effective, and patient-centered approach to IBD management[44].

Telemedicine allows for contact with remote patients, enhancing disease treatment. Patients can attend meetings virtually, decreasing travel problems and associated costs. Tools like MyIBDcoach allow real-time symptom tracking and enable healthcare providers to immediately respond to any changes in a patient's condition, leading to fewer outpatient visits without compromising safety. Telemedicine also enhances patient education by providing online resources. This self-management supports adherence to medication and may reduce flare-ups and hospital admissions[37]. The role of specialized IBD nursing within telehealth is becoming increasingly important for comprehensive care. Telenursing programs efficiently address barriers to medication adherence through remote follow-ups, enhancing compliance. As technology advances, its application in IBD management is expected to grow, potentially combining advanced telemonitoring tools with predictive analytics for flare-ups. This progress could transform IBD treatment, enabling personalized, data-driven strategies tailored to individual patient needs[39].

Collaborative efforts in the medical community

Collaboration in healthcare is essential for enhancing drug delivery systems and providing better care for individuals with IBD. Managing IBD requires a comprehensive approach involving gastroenterology, rheumatology, nutrition, and psychology to deliver individualized care. Collaborative frameworks among healthcare professionals improve information sharing, leading to increased diagnostic accuracy and treatment outcomes[43,44].

Telemedicine platforms have emerged as a significant tool, facilitating real-time communication between patients and healthcare providers. These systems also provide clinicians with valuable insights into patient conditions[39]. Cross-institutional collaborations further enhance knowledge sharing, particularly through multidisciplinary video conference education sessions where various specialists discuss best practices in IBD management. This collaborative framework improves provider education and fosters a supportive environment. Involving patients is essential; their feedback about treatments and telehealth services can guide advances in care delivery. Engaging them in research confirms that their perspectives influence clinical practices and innovations. Additionally, collaborative research is crucial for assessing the

long-term safety and effectiveness of new drug delivery techniques for IBD[43,44].

CONCLUSION

The management of IBD has changed throughout the years with advances in molecular understanding and clinical practice. This review highlights recent improvements in IBD management. The review also addressed the transition from conventional treatments to novel treatments, including microbiome-based interventions, biologics, small-molecule inhibitors, and personalized medicine approaches. Through better precision and decreased systemic toxicity, these strategies aim to improve disease control and enhance patient quality of life.

As small molecules and biologics become more widely used, the treatment options for IBD continue to evolve, each having its own advantages and disadvantages. Unlike small molecules, which offer a suitable oral route and may be used in combination therapies, biologics are susceptible to inducing immunogenicity, despite their efficacy. Oral drug administration continues to be complicated for IBD patients, and the long-term safety of these new drugs is still unknown. The development of customized treatment plans is crucial due to the complex nature of IBD, which includes medication responses, patient compliance, and genetic predispositions. These strategies should take into consideration each patient's profile, desired administration routes, and medical and personal family history.

Regardless of advancements in IBD therapy, many restrictions persist, such as the financial strain of chronic treatment, primary non-response, secondary loss of efficacy, and long-term safety issues. Furthermore, the need to customize treatment based on pharmacogenetics, specific patient variables, and predictive biomarkers is underscored by individual genetic and immunological profiles. Innovations in drug delivery systems, such as smart stimuli-responsive nanocarriers, have the potential to enhance adherence, bioavailability, and targeted distribution, particularly in noncompliant populations.

Moreover, telemedicine, AI, and digital technology integration hold promise for revolutionizing IBD monitoring and treatment by reducing the burden on healthcare systems and enabling remote management and early intervention. To ensure equitable access to care and translate these advances into clinically significant outcomes, collaborative, interdisciplinary efforts are essential. Ultimately, the future of IBD treatment hinges on the integration of innovation, customization, and accessibility. IBD must be transformed from a chronic disease into a manageable condition with optimal long-term outcomes through consistent investment in medical research and patient-centered healthcare strategies.

FOOTNOTES

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MINIREVIEWS

Evolving ethos of medical research: A retrospective analysis of the declaration of Helsinki (1964-2024)

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Abstract

The World Medical Association's Declaration of Helsinki (DoH) serves as a key document of ethical guidance advocating principles of medical research involving human participants. Since its inception in 1964, the DoH has undergone several revisions, reflecting a dynamic evolution in our understanding of research ethics, spurred by gaps identified within the document, harms discovered, challenges identified during ongoing research activities, scientific advancements and societal shifts in values. The DoH addresses a challenge and a conflict that may arise between two key aspects of medical research: On one hand, the fundamental obligation of physicians to do no harm, and on the other, the essential need to ensure the efficacy and safety of medical interventions by testing them on human research participants or healthy volunteers. With each revision, increasing emphasis is given to distributive justice and beneficence and not only to patient autonomy. Despite being a comprehensive and concise document, occasional criticism is reported, such as with regards to the impracticability of obtaining informed consent amongst other challenges. This essay will examine the key changes across the DoH's iterations, highlighting the progressive strengthening of participant protection and the evolving relationship between research, societal benefit, and individual rights.

Key Words: Ethics; Declaration of Helsinki; World medical association; Medical research; Informed consent

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Core Tip: The current 2024 revision of the Declaration of Helsinki (DoH) marks the 11th version of the DoH since its inception in 1964. Throughout the past 60 years, many notable controversies in medical ethics have arisen, such as the Tuskegee syphilis study and the harvesting of the HeLa cell line. Following these incidents, iterations of the DoH have increasingly emphasized distributive justice and beneficence, rather than focusing solely on patient autonomy. This essay will examine the key changes across the DoH's iterations, highlighting the progressive strengthening of participant protection and the evolving relationship between research, societal benefit, and individual rights.

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INTRODUCTION

Medical research is a vital component of clinical medicine and serves as a cornerstone for driving advances in the cure and control of diseases. Throughout history, humanity has engaged in human experimentation. Notably, in 1796, Edward Jenner observed that milkmaids who had cowpox appeared to be immune to smallpox, prompting him to conduct a controversial experiment. He inoculated 8-year-old son of his gardener, James Phipps, with cowpox pus and then deliberately exposed him to smallpox to test immunity. This groundbreaking work laid the foundation for modern vaccination practices and ultimately contributed to the control of smallpox. Lack of informed consent, vulnerability, and severe risk of intentional harm make Jenner's experiment unethical by current standards. But Jenner received numerous accolades and gifts from King Charles III, Napoleon, empress of Russia, was given GBP 30000 by the parliament for his contributions towards public health and conferred an honorary Doctor of Medicine degree by the University of Oxford. About 150 years later, public trust was fractured in revelation of horrific ethical failures of physicians during World War II. The Declaration of Helsinki (DoH) was set up to reaffirm the norms of medical research and practice that must apply to all doctors and to prevent breaches of ethical conduct among physicians in the future, but most importantly, to reestablish patient trust for physicians[1]. The principles in DoH were largely adopted from the Nuremberg Code[2]. The DoH is a living core document that stands as a cornerstone of ethical guidance advocating principles of medical research involving human participants. Since its inception in 1964, the DoH has undergone several revisions (Figure 1), reflecting a dynamic evolution in our understanding of research ethics, spurred by gaps identified within the document, harms discovered, challenges identified during ongoing research activities, scientific advancements and societal shifts in values. The DoH addresses a challenge and a conflict that may arise between two key aspects of medical research: On one hand, the fundamental obligation of physicians to do no harm, and on the other, the essential need to ensure the efficacy and safety of medical interventions by testing them on human research participants (for therapeutic research) or healthy volunteers (for non-therapeutic research). The DoH attempts to set the balance right. The DoH was written and is written by physicians. So, it's firstly and foremost, a moral obligation for physicians, although the world medical association (WMA) has always invited other healthcare professionals and researchers to adopt these principles. With each revision, increasing emphasis is given to distributive justice and beneficence and not only to patient autonomy. This essay will examine the key changes across the DoH's iterations, highlighting the progressive strengthening of participant protection and the evolving relationship between individual rights, scientific research, and societal benefit.

THE GENESIS OF THE DECLARATION OF HELSINKI (1964)

The 1964 version established a relatively simple framework with five basic principles. It emphasized the physician's duty to safeguard the health of the people and introduced the crucial concept of prioritizing the patient's well-being over scientific advancement. The primary obligation of the physician is to the patient, and DoH makes a reference to both Declaration of Geneva as well as International Code of Medical Ethics. DoH acknowledges a physician's duty to promote and safeguard the health, well-being, and rights of patients, including those who are involved in medical research. It reaffirms that while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research participants. Jerry Menikoff highlights the conflict of interest with inherent tension between prioritizing individual patient well-being (clinical practice) and scientific research [3]. However, this tension is not an ethical failure, but a challenge addressed by DoH that weigh competing (not conflicting) interests by recommending principles and processes to ensure participant safety and ethical research conduct. The 1964 version was narrow in its scope to include clinical research on subjects. Over the various revisions, the scope is broadened to include medical research, including research on identifiable human material and data and the human subjects are accorded agency and dignity by rephrasing as participants. Measures such as disclosing conflicts of interest, establishing independent oversight, free and informed consent, funding transparency, and meaningful engagement serve to maintain patient and public trust to participate in research. Furthermore, the language regarding informed consent was less explicit and it was detailed in subsequent versions. The document lacked the nuanced considerations for vulnerable populations and did not address the potential for structural inequities to influence the distribution of risks and benefits.

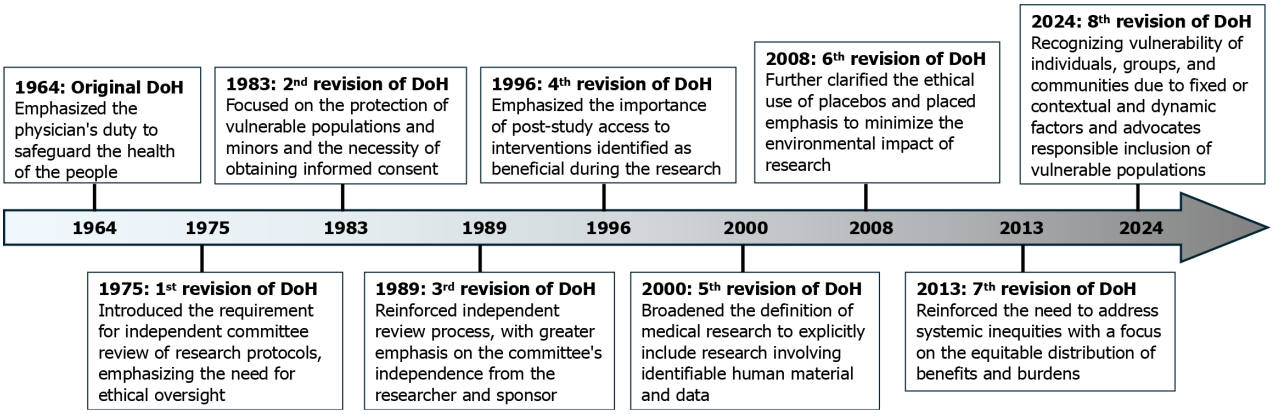


Figure 1 Timeline of the declaration of Helsinki document versions. DoH: Declaration of Helsinki.

The role of independent ethical review was absent, empowering physician with responsibility and professional judgment. This reflected the prevailing medical ethos of the era, *i.e.* physician paternalism.

THE 1975 REVISION: A PIVOTAL SHIFT TOWARDS INFORMED CONSENT

The 1975 revision, drafted by three Scandanavian doctors, marked a significant leap forward with emphasis on the independent review of research protocols, prioritizing the well-being of research participants above the interests of science, and enhancing requirements for informed consent[4]. This change was a direct response to previous unethical practices. This was following the media coverage of the disreputable Tuskegee syphilis study conducted from 1932 to 1972, where African American men participating in the study were not informed about their syphilis diagnosis, and were not treated even when penicillin became standard of care in 1947. 399 men with syphilis and 201 uninfected males were enrolled into the study believing that they would receive treatment for any diagnosed illnesses. Several of these men were subjected to lumbar punctures under the impression that it was therapeutic and suffered complications[5]. Eventually, 28 men died of syphilis, and another 100 dying of related complications[6]. Similarly, the Willowbrook state school study took place between 1956 to 1972, and involved the intentional infection of children with developmental disabilities with hepatitis by feeding them with hepatitis virus titrated from stool samples[7]. This was done to study the progression of the disease and investigate the possibility of developing a hepatitis vaccine[8]. Subsequent studies then determined that these individuals were infected with hepatitis A and B, with several inoculated individuals developing jaundice as a result[9]. Exploitation of vulnerable groups, lack of informed consent, and disregard for disproportionate risk of harm render this comparable to Jenner's experiment. No longer a mere mention, informed consent became a central tenet, demanding that participants receive comprehensive information regarding the study's purpose, procedures, risks, and potential benefits, enabling them to make a truly autonomous decision about participation. The revision also explicitly addressed the need for ethical considerations regarding environmental protection and the treatment of animals used in research, while stipulating that the DoH itself should be subject to ongoing review. Aside from echoing patient autonomy, the 1975 version also underscored the importance of independent ethical review, laying the foundation for institutional review boards (IRBs) or Ethics Committees to oversee research protocols, providing an external check on research integrity and protecting participant rights. These independent ethics committees are entrusted with maintaining checks and balances on researchers' pursuits, as they stand to benefit from the research through enhanced professional and personal reputations, improved career prospects, and increased remuneration. This revision implicitly acknowledged the need for more robust protections of vulnerable populations, though it lacked explicit guidelines for these specific groups. Table 1 provides a summary of key highlights of each DoH version.

FURTHER REFINEMENTS (1983-1996): STRENGTHENING PROTECTIONS AND CLARITY

The 1983, 1989, and 1996 revisions built upon the 1975 foundation, refining existing principles and enhancing clarity. In 1983 there were fairly minor changes to the text of the DoH[10]. For example, the word 'doctor(s)' was changed to 'physician(s)', the Latin phrase a forteriori was changed to 'especially'. In addition, there was rewording of quote from the International Code of Medical Ethics and consent for minors. In the 1989 version, the independent review process was reinforced, with greater emphasis on the committee's independence from the researcher and sponsor. The focus on protecting the integrity of participants and ensuring their privacy became more explicit, addressing concerns about potential coercion and undue influence. The first time the DoH refers to any specific type of research methodology, *i.e.* the placebo-controlled trial, was its 1996 version. While the 1964 version briefly mentioned vulnerable populations, the subsequent revisions gradually refined the guidelines for their protection. For example, the AIDS Clinical Trials Group published trial results on the usage of zidovudine in the 1994s in Africa. These trials in Africa were highly controversial,

Table 1 1964-2024 versions of declaration of Helsinki with key points

Month, year	City, country	WMA general assembly	Remarks
June, 1964	Helsinki, Finland	18th	First version of the guiding principles of clinical research by international collaboration mentions 'freely given consent' from patient
October, 1975	Tokyo, Japan	29th	(1) Clinical research changed to biomedical research; (2) Patient – changed to human subjects; (3) Consent – changed to informed consent with mention of written consent; (4) Introduced concept of doctor-patient relationship; (5) Strengthened protection of vulnerable populations; (6) Oversight of specially appointed independent committee (concept of Institutional Review Boards); and (7) Guidance on publication of research
October, 1983	Venice, Italy	35th	(1) Doctor – changed to physician; (2) Minor assent/consent emphasis if applicable; and (3) Subjects termed as volunteers for non-therapeutic research
September, 1989	Hong Kong	41st	(1) The independent committee should have impartial oversight to minimize conflict of interest; and (2) The independent committee should be free from the influence of both the researcher and the sponsor
October, 1996	Somerset West, RSA	48th	(1) Emphasis on the wellbeing of the patient/subject; (2) The responsibility extends beyond obtaining informed consent, including monitoring for safety and welfare; (3) Adds a clarification - use of placebos is acceptable in studies only when there is no proven diagnostic or therapeutic method; and (4) Reinforces the need for extra caution when obtaining informed consent in vulnerable populations
October, 2000	Edinburgh, Scotland	52nd	(1) Replaced 'biomedical' with 'medical' and explicitly includes research on identifiable human material and data; (2) Highlights the challenges of obtaining consent from individuals who may be under duress or coercion; (3) The role and responsibilities of independent ethics committees are expanded; (4) Adds the condition that the research should only be done if the population involved will directly benefit from the research findings; and (5) In publication, stresses the necessity of transparency by including information on funding, sponsors, and potential conflicts of interest
October, 2002	Washington DC, United States	53rd	(1) Clarification of placebo use - a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under specific circumstances
October, 2004	Tokyo, Japan	55th	(1) Clarification on post-trial access - Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review
October, 2008	Seoul, Republic of Korea	59th	(1) Regarding vulnerable populations, it reiterates that research is only justified when it directly addresses their health needs and there's a reasonable likelihood of benefit; (2) Enhances the authority and responsibilities of ethics committees; (3) Mandates that all clinical trials must be registered in a publicly accessible database before the enrolment of the first participant. This improves transparency; and (4) Re-emphasizes the importance of publishing both positive and negative findings and reporting conflicts of interest in research publications
October, 2013	Fortaleza, Brazil	64th	(1) Emphasizes the importance of transparency and public access to research data; (2) Explicitly states that the research ethics committees must have the authority to monitor ongoing studies and ensure that the researchers provide timely and complete information, especially regarding serious adverse events; (3) Biobanks included alongside identifiable human material and data; and (4) Compensation must be provided to research participants who are harmed as a result of participating in a study
October, 2024	Helsinki, Finland	75th	(1) Broadened accountability for all individuals, teams, and organizations; (2) "Subject" replaced by "participant" for autonomy and engagement; (3) Inclusion of healthy volunteers as participants; (4) "Informed consent" changed to "free and informed consent"; (5) Emphasis on community consultation and engagement; (6) Emphasizes meaningful engagement with participants and their communities before, during, and after the study; (7) Essential to uphold principles during public health emergencies; (8) Promoting environmental sustainability; and (9) Substantial changes in vulnerability section

as the control groups were given a placebo drug despite availability of effective drugs that prevent vertical transmission of human immunodeficiency virus[11]. This incremental development reflects a growing awareness of the potential for exploitation of vulnerable populations and a greater recognition of the need for proactive measures to prevent harm. Figure 2 summarises the structural details of the various DoH versions. It is evident that the document has ballooned to four time its original word count.

THE 2000 DECLARATION: AN INCLUSIVE APPROACH

The 2000 declaration represented a watershed moment with only three of the 32 paragraphs unchanged and eight new paragraphs added. The introduction of this version recognizes the conflict between advancing medical practice through research (by challenging existing methods) and ethical obligation to protect research participants from exploitation, particularly vulnerable populations. The previous versions dichotomized research into therapeutic and nontherapeutic, but the 2000 version broadened the definition of medical research to explicitly include research involving identifiable human material and data[12]. The revision of DoH was driven by overall scientific trends and multiple incidents during the time, one being the HeLa cell line controversy, in which Henrietta Lacks' tumor cells were harvested and propagated

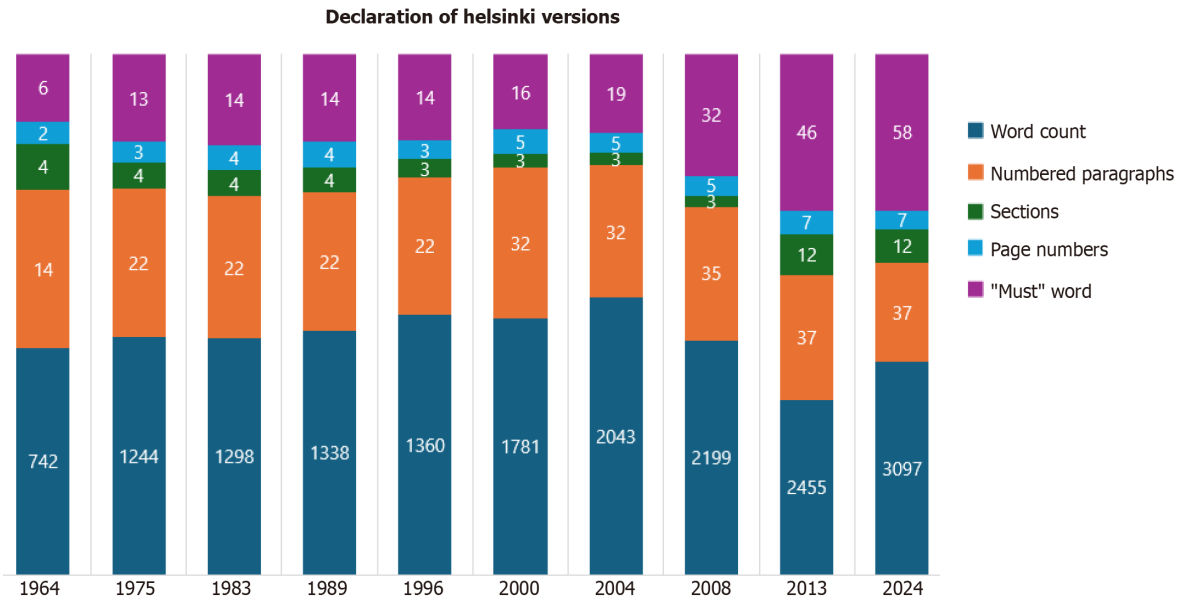


Figure 2 Structural details of the declaration of Helsinki document versions by years. Word count was generated using https://www.montereylanguages.com/pdf-word-count-online-free-tool.html (Accessed on January 7, 2025).

without her or her family's consent for the usage of biomedical research[13]. As the HeLa cells provided to researchers were readily identifiable, Henrietta Lacks' genetic information could be disclosed. In addition to the lack of informed consent, Lacks' family were not informed regarding the use of these cells in medical research for decades, and received no compensation as a result[14]. This episode highlighted the importance of taking informed consent from individuals, including human biospecimens such as cells or genomes.

In addition to the above changes, this revision reworded 'biomedical research' to 'medical research' and strengthened the emphasis on equitable access to participation in research, acknowledging that historically marginalized communities were often underrepresented. Another aspect of the revision includes a significant clarification and expansion of the placebo cause, stating that researchers should offer the best-known therapy available instead of a placebo, with the exception being when no proven or effective treatment exists. However, Tollman *et al*[15] argued that the placebo clause may inadvertently hinder research in resource-constrained settings due to the demands it places on already weak healthcare systems. While this may hold true, it is crucial to prioritize patient welfare, as providing the best-known therapy not only upholds research integrity but also ensures that participants receive optimal care. The principles governing informed consent were further refined, with more specific considerations for vulnerable populations and those lacking capacity for autonomous decision-making. The concept of proxy consent was further developed. This marked a significant shift towards a more inclusive and equitable approach, aiming to address existing societal disparities and promote fairness in research participation. However, the concept of Gillick competency has not been acknowledged in DoH and Hilda Bastian has considered this as a "step backwards for people who are legally 'incompetent' to make their own decisions (including those under 18years old) but who are in fact capable of doing so"[15]. While the declaration may be viewed as restrictive, it is essential to ensure that the protection of vulnerable populations, including those deemed legally incompetent, is prioritized to prevent harm and safeguard their rights within the research process. As WMA is not prescriptive document, within the governance of local ethical and regulatory framework, research may be conducted in legally incompetent persons. Lastly, the WMA has set strict tone to global institutions that rich populations should not exploit poor populations: "...research should not be carried out in countries in development just because it is cheaper and the laws are more lax"[16].

CLARIFICATIONS AND ENHANCEMENTS (2002-2004): PRECISION AND POST-TRIAL ACCESS

The 2002 and 2004 versions were primarily focused on clarifying existing guidelines. In 2002, a note of clarification was added by the WMA saying that placebo control may be ethically acceptable even if proven therapy is available if two conditions are met: (1) If there are compelling and scientifically sound methodological reasons; or (2) If patients would not be subject to any risk of serious or irreversible harm. Back then, these two conditions were linked with an 'or'. A few years later in 2008, this note of clarification was removed and this wording was then changed and put into the main document. The two conditions were linked with an 'and' instead of an 'or'. Furthermore, the phrase 'extreme care must be taken to avoid the abuse of this option' was added in 2008, which serves to add additional protection for study participants. The 2004 version also emphasized the importance of planning for post-trial access to any benefits identified during the study. These refinements reflect a continuous effort to ensure study participants receive appropriate timely access to medical care.

THE 2008 DECLARATION: BROADER SOCIETAL CONTEXT AND SUSTAINABILITY

The 2008 Declaration introduced even more significant changes, emphasizing the importance of considering the broader societal context of medical research. It explicitly called for researchers to consider the ethical, legal, and regulatory norms in their countries and internationally, while stressing that national regulations should not diminish the protections for research participants. The 2008 version also placed emphasis to minimize the environmental impact of research.

THE 2013 DECLARATION: PARTICIPANT-CENTRIC APPROACH AND SYSTEMIC INEQUITIES

The 2013 Declaration further strengthened the participant-centric approach, explicitly stating that the well-being of the individual research participant must take precedence over all other interests. The "responsiveness principle" mandates that studies address local health needs, fairly select participants, and ultimately benefit the community through improvements in healthcare, economic activity, and research capacity building[17]. It reinforced the role of research ethics committees (RECs) in the oversight of research, granting them greater autonomy and emphasizing their responsibility to monitor ongoing studies. The 2013 version also reinforced the need to address systemic inequities with a focus on the equitable distribution of benefits and burdens.

THE 2024 DECLARATION: A COMMITMENT TO EQUITY AND TRANSPARENCY

The 2024 Declaration represents the most recent iteration that fruited following a two year inclusive process of regional and topical meetings (Table 2) by the working group of members from 19 countries, formed in April 2022. This was followed by two phases of general public feedback and comment gathering and is an incremental evolution rather than revolution. The 2024 version changed the preamble to include participants rather than subjects to respect rights and agency. The latest version also advocates that principles should be upheld by all individuals, teams, and organizations involved in medical research. It emphasizes the importance of 'free and informed consent' so research participants can make decisions free from undue influence[18]. In addition, protection of vulnerable populations, avoiding research waste, and the role of RECs, also introduces several significant shifts. The 2024 version mentions recognizing vulnerability of individuals, groups, and communities due to fixed or contextual and dynamic factors. It advocates responsible inclusion of vulnerable populations by not depriving them from the important benefits of participation in research. It emphasizes meaningful engagement with participants and their communities, advocating for their input at all stages of research, from design to dissemination. It directly addresses the problem of structural inequities, calling for conscious effort to avoid perpetuating or exacerbating social inequalities. The 2024 version advocates for resourceful and independent ethics committee with diversity of members who has received necessary education, qualifications, and training. It places a heavy emphasis on transparency, particularly in data sharing and publishing results, and on ensuring post-trial access to any benefits arising from the research (Figure 3). This version reflects a deeper understanding of how societal factors can influence the ethical conduct of research and a strong commitment to creating a more equitable and just research environment.

CONCLUSION

Critical analysis and future directions

The DoH despite being a comprehensive and concise guiding document, occasional criticism is reported. Dal-Ré[19] has reported that DoH guidelines fall short of certain situations where it is impracticable to obtain informed consent, such as in emergency medicine. The Council for International Organizations of Medical Sciences (CIOMS) is an organization that works with the World Health Organization to develop ethical guidelines for health-related research involving humans. These guidelines are widely used and often serve as a reference point for national regulations and research ethics committees worldwide, especially Australia, Canada, and United States. According to CIOMS, a REC may approve a modification or waiver of informed consent to research if: (1) The research would not be feasible or practicable to carry out without the waiver or modification; (2) The research has important social value; and (3) The research poses no more than minimal risks to participants. The 2024 DoH version does not mention the three conditions and empowers the local RECs, *i.e.* DoH is not prescriptive and it is consistent with its intent and purpose of providing broad guiding principles that has to be applied and interpreted by research teams under institutional governance framework.

In fact, one of the key features of DoH is that it is not a detailed rulebook! The revised versions have more uncontroversial principles and guidelines and less controversial aspects. The absence of globally recognized ethical standards for forensic research using human cadavers and remains has garnered traction for application of DoH principles responsible practice by forensic scientists[20]. Similarly, Ashall *et al*[21] has highlighted the potential of adapting the ethical principles outlined in the DoH to create an internationally agreed best practice in clinical veterinary research.

While the 2024 Declaration commendably broadens its scope, controversy and debate are inevitable as the declaration takes on complex ethical issues with inherent conflicts[22]. Significant omissions remain. The lack of explicit guidance on embryo research, particularly given evolving understandings of personhood[23], alongside the superficial treatment of animal research (limiting itself to a general statement on welfare and neglecting the 3Rs principle), reveal crucial gaps as

Table 2 Regional and topical meetings convened for 2024 revision

City	Topic
Tel Aviv	Implications of big data, machine learning, artificial intelligence
Sao Paulo	Ethical considerations on use of placebo
Copenhagen	Emerging trial designs
Tokyo	Research during public health emergencies/pandemics
Vatican	Research in resource-poor settings, global justice
Johannesburg	Community inclusiveness, post-trial access, vulnerability
Munich	Specific and particularly vulnerable groups
Washington DC	Final consolidation

Adapted from: https://www.youtube.com/watch?v=hvcQ1hj_Xqs&t=2796s (Accessed on January 6, 2025).



Figure 3 Key elements of the declaration of Helsinki.

animals are fellow creatures with dignity, and animal deaths do matter morally[24,25]. Further, the Declaration's narrow focus on medical research overlooks the ethical challenges inherent in non-medical health research, including studies on social determinants of health and genetic research, where the heritable nature of data raises unique concerns about individual autonomy and broader societal impact. Expanding the scope to encompass all health research with human participants, as suggested by Saenz *et al*[26], would enhance its relevance and impact, particularly in low- and middle-income countries. The growing interconnectedness of data and potential privacy issues necessitate attention to cybersecurity. The next iteration of the DoH may need to explicitly address the evolving role of data security and responsible data sharing. Furthermore, the Declaration's emphasis on autonomy presents significant challenges for high-risk research, such as that conducted in intensive care units, where surrogate consent is often compromised[27]. The variability of REC standards may exacerbate these issues. Last but not least, the DoH will have to consider ethical implications of artificial intelligence, health economics, and scientific publishing.

In the work of senior author as a researcher, research mentor, and chairperson of Institutional Animal Care and Use Committee, he has found the DoH to be an invaluable guide in designing research protocols, training researchers, and conducting ethical reviews. Its emphasis on participant autonomy, transparency, and equity has significantly influenced his approach to obtaining informed consent, minimizing risks, and ensuring equitable benefit sharing. The continuous evolution of the DoH in response to emerging societal trends and scientific advances remains an inherent strength of DoH.

In conclusion, DoH is the first amongst the equals in medical research ethics considerations[28]. From a relatively basic framework focused primarily on physician responsibility, the DoH has evolved into a comprehensive document that places the well-being and rights of research participants at its core. The increasing emphasis on free and informed

consent, protection of vulnerable populations, transparency, and equity reflects a commitment to ethical research practices that prioritize both scientific progress and social justice. The revised document does not replace the roles of the IRBs in reviewing and approving all research study protocols[29]. Though, the influence and relevance of DoH has been questioned due to availability of other ethical guidelines and codes of practices, the ongoing revisions demonstrate a commitment to adapt to the ever-changing medical research landscape ensuring that scientific progress remains ethically sound and socially responsible[30].

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of depression on functional status in elderly patients undergoing total knee arthroplasty

Tomas Ignacio Nicolino, Maximiliano Smietniansky, Bruno Boietti, Ignacio Garcia-Mansilla, Lisandro Carbo, Cintia Belen Martinez

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Abstract

BACKGROUND

The prevalence of depressive symptoms in patients undergoing total knee arthroplasty (TKA) ranges from 22% to 26%. The impact of depression on functional status post-TKA remains controversial.

AIM

To be the first study in Latin American population to evaluate the association between depression and functional status one year after TKA, hypothesizing that elderly patients with depression will demonstrate lower rates of functional improvement.

METHODS

We conducted an observational, descriptive and analytic, retrospective cohort study involving patients over 65 years old who were indicated for TKA. Assessments were made *via* the Program for Determination and Management of Risks for Practices and Procedures of the Division of Geriatric Medicine at the Italian Hospital of Buenos Aires, between June 2015 and July 2019. Depression screening was conducted using Yesavage's abbreviated score and Patient Health Questionnaire-9, while functional ability was evaluated using the Knee Society Score (KSS).

RESULTS
Of the 100 patients analyzed, 22 (22%) screened positive for depression. The mean age was 80 years ± 6.3 years, with an average of 77.6 years ± 6 years in the depressed group and 80.6 years ± 6.3 years in the non-depressed group (P = 0.05). Depressed patients showed significantly greater cognitive impairment [clock-face drawing test median: 5 (3-6) *vs* 6 (5-7), P = 0.06] and more risk factors for confusional syndrome (mean: 8 ± 2 *vs* 6.5 ± 2.2, P = 0.006). Frailty was also more prevalent in depressed patients [Edmonton: 15 (68%) *vs* 33 (42%), P = 0.05; Fried: 17 (77%) *vs* 42 (54%), P = 0.05]. Postoperative Functional KSS were similar between groups (depressed: 65 ± 22.1 *vs* non-depressed: 66.3 ± 20.3, P = 0.8). Linear regression analysis revealed no association between depression and changes in KSS. Spearman's rank correlation coefficients were -0.0304 (P = 0.8) for Functional KSS variation and -0.1 (P = 0.3) for KSS variation.

CONCLUSION
Depression in patients with osteoarthritis should not hinder surgical planning. Identifying and treating depression preoperatively may enhance outcomes such as pain relief and reduce risks of acute confusional syndrome, cognitive impairment, and frailty.

Key Words: Elderly adults; Knee osteoarthritis; Depression; Functional statu; Total knee arthroplasty

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Core Tip: This study evaluates the relationship between depression and functional outcomes one year after total knee arthroplasty (TKA) in elderly patients. Results indicate that while depressive symptoms are common, they do not impact functional recovery as measured by the Knee Society Score. However, depression correlates with greater cognitive impairment, increased frailty, and higher risk of confusional syndrome. These findings suggest that depression should not be a barrier to TKA, though preoperative identification and management of depressive symptoms may improve postoperative quality of life and reduce complications.

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INTRODUCTION

Total knee arthroplasty (TKA) is the standard of care for the relief of severe osteoarthritis-associated knee pain that is refractory to non-surgical treatments. This procedure is widely accepted and consolidated in the field of orthopedics. Although pain is influenced by multiple factors, mental health disorders are often present alongside pain and tend to be linked with poorer outcomes. The prevalence of depressive symptoms in patients undergoing TKA ranges between 22%-26%[1]. Over the past years, several authors have defined depression as an independent variable for the prediction of TKA postoperative outcomes in elderly patients. Nonetheless, other authors have reported that depression does not appear to hurt outcomes[2]. Research addressing the impact of depression on functional status in TKA is scarce.

We must consider that many patients undergoing knee arthroplasty present a condition of frailty in their baseline health status. Fragility, or frailty, is a clinical syndrome characterized by a decline in physiological reserve and increased vulnerability to stressors, often manifesting as weakness, weight loss, exhaustion, and reduced physical activity. In contrast, cognitive impairment refers specifically to a decline in cognitive functions such as memory, reasoning, and problem-solving abilities. While both conditions are associated with aging and can lead to increased health risks, frailty primarily affects physical health and resilience, whereas cognitive impairment impacts mental processes and daily functioning. Understanding these differences is crucial for developing appropriate interventions and support for affected individuals.

A recent study by Gebauer *et al*[3] found no link between depression and the timing of TKA. However, surgeons should still assess patients for depression and its symptoms, as it is a common comorbidity that could affect postoperative outcomes. An observational study from a Swedish registry involving 8745 patients found that both preoperative and postoperative patient-reported anxiety or depression heighten the risk of dissatisfaction after TKA, even when pain and function improve[4]. Ensuring patients receive appropriate treatment for depression may be crucial for achieving favorable surgical results. Patients with anxiety or depression may struggle to participate fully in rehabilitation and experience poorer outcomes in terms of pain and function. Consequently, it remains uncertain whether the risk of dissatisfaction in these patients is due to their worse pain and functional outcomes or if the anxiety or depression itself plays a significant role[5].

We performed an observational, descriptive, analytic, retrospective cohort study to study the association between depression and functional status one year after TKA in patients over 65 years of age. We hypothesized that elderly patients with depression would have lower rates of functional improvement after one year in comparison to patients without depression. The demographic characteristics and the presence of geriatric syndromes in our patient population were evaluated, as well as the association between depression and major complications or death at three months post-surgery.

We also aimed to explore the association between depression and length of hospital stay, readmission, number of required sessions of physical therapy, and consultations with the surgical team.

MATERIALS AND METHODS

Study design and patients

We included patients over 65 years of age with an indication for TKA that were assessed by the Program Determination and Management of Risks for Practices and Procedures (DRIPP) of the Division of Geriatric Medicine of the Hospital Italiano of Buenos Aires (HIBA) before surgery between June 2015 and July 2019. Patients were required to receive surgical treatment within three months of initial evaluation. A specific team of orthopedic surgeons from the Division of Arthroscopic Surgery and Knee Prosthetics of the Department of Orthopedics and Traumatology of the HIBA performed all surgeries.

Patients were excluded from the study if they were planning to undergo procedures requiring additional procedure to total knee prosthesis (osteotomy, extensor mechanism realignment, or osteosynthesis), knee revision surgery, simultaneous bilateral arthroplasty, or if the prespecified surgical team did not perform surgery.

The Department of Orthopedics and Traumatology performs a monthly average of 600 surgeries, many of them being complex procedures such as joint reconstruction, spine and oncologic surgery. The DRIPP program was developed within the Department of Geriatric Medicine, and through it, approximately 700 patients are assessed per year. Since its establishment in 2013, over 2500 patients have been evaluated in both outpatient and inpatient settings. Typically, DRIPP assessment consists of a comprehensive clinical and geriatric evaluation of patients undergoing intermediate or high-risk surgical procedures, as well as oncologic treatment regimens (chemotherapy, radiation, or high-cost biologic drugs and targeted therapies). Clinical comorbidities are included in the analysis, but the main scope of assessment is the detection, qualification, quantification, and management of each patient's biological and psychosocial risk. The program works in a transdisciplinary fashion to achieve effective communication, produce an impact on decision-making, enhance the process of informed consent, decrease morbidity and mortality as well as improve each patient's functionality outcomes and global quality of life. Every aspect of patient care is carefully documented and stored within a centralized digital registry that includes a unique medical record and history for everyone.

In this study, patients referred for DRIPP assessment presented at least one of the following criteria for geriatric vulnerability: (1) Polypharmacy (according to Beers' criteria[6]; (2) Functional impairment (defined if the patient requires assistance to perform any of the following activities, including meal preparation and feeding, handling finances, taking medication, shopping for groceries, or travelling alone by any means of transport); (3) Nutritional risk (loss of more than 5% body weight over the past year); (4) General health status (2 or more hospital admissions over the past year); (5) Risk of cognitive impairment (difficulty in understanding medical indications); (6) More than two clinical comorbidities; and (7) Dementia or Parkinson's Disease.

The program entails the exploration of functional ability through the assessment of the following domains: (1) Basic activities of daily living and instrumental activities of daily living[7], evaluation of disease burden through Charlson's comorbidity index, polypharmacy and potentially inappropriate medication; (2) Gait alterations and sarcopenia, nutritional status by mini-nutritional assessment[8]; and (3) Frailty according to Edmonton[9] and Fried[10], as well as screening for cognitive impairment[11], risk factors for acute confusional syndrome and depression. Life expectancy is also estimated by use of the PROFUND[12], Lee *et al*[13] and Schonberg *et al*[14] scores.

Once the evaluation is complete, geriatric specialists design specific interventions based on the findings. Chronic medication is listed and reviewed, and potentially inappropriate medication is gradually tapered or suspended. Detection of chronic clinical comorbidities allows for patient optimization if necessary. Alcohol consumption is discouraged and smoking cessation counseling is provided as needed. Malnourished or at-risk patients receive nutritional consultation. Both patients and care providers receive recommendations for the prevention of falls. Patients with high fall risk or sarcopenia are referred to physical therapy for optimization prior to the planned intervention (prehabilitation). Another important aspect of DRIPP assessment is screening for social geriatric risk. Vulnerable patients with debilitated or fragmented social support networks are enrolled for long term clinical follow-up by specialists in geriatric medicine.

Outcomes and definitions

Concerning the main aim of this study, screening for depression was performed by using two scales: (1) Yesavage's abbreviated score (used from 2013 through 2016); and (2) Patient Health Questionnaire-9 (PHQ-9) (used from 2017 to present). The PHQ-2 questionnaire comprises two specific questions that interrogate the presence of anhedonia and dysphoria, which are both diagnostic criteria for major depressive episodes. Positive answers have 96% sensitivity and 57% specificity for the diagnosis of depression. A negative answer to both questions proves depression to be very unlikely, with a probability index of 0.07 and a subsequent probability of 2%. In this study setting, we considered patients with two positive answers to be depressed[15].

Yesavage's Geriatric Depression Scale is an instrument that is widely used for depression screening in patients over 65 years of age[16]. In 1986, Yesavage and Sheikh[17] proposed an abbreviated version of the original test, which is composed of 15 questions. It maintains the classic "yes or no" format, but has greater application feasibility. A score of 5 or more positive answers suggests the diagnosis of depression. Both the original and the abbreviated questionnaire discriminate between depressed and non-depressed patients with excellent correlation ($r = 0.84$, $P < 0.001$)[17].

Functional ability was assessed using the Knee Society Score (KSS)[18] which is divided into two components. The first component assesses the knee clinically through physical examination, and includes the evaluation of pain, stability and range of movement with a resulting score that ranges from 0 to 100, 0 being the lowest score and 100 the highest. The second component assesses the individual's functionality, with the same value range.

Data collection

Information was extracted through manual revision of the electronic medical records of patients planning to undergo TKA who were referred for DRIPP assessment prior to surgery during the aforementioned period. All of the study data was handled with maximum confidentiality and patient anonymity was preserved in all cases. The obtained data was transferred to a numerically coded database which was later processed and analyzed. Access to the database was restricted to the study investigators.

Exposure variables (depression), result variables (Knee Society functionality scores and combined event of death or major complication at 3 months) and clinical baseline variables were operationalized (Table 1).

Statistical analysis

For the descriptive analysis, continuous variables were expressed in means with the corresponding SD, or as medians and interquartile range, according to distribution. Categorical variables were expressed as percentages in absolute numbers.

The study population was divided into two groups according to whether they screened positive for depression. For categorical variables, χ^2 or Fisher were applied as needed, and for continuous variables, t test or Mann Whitney were used according to normal distribution. For our secondary endpoint analysis, association with age was estimated as a continuous variable through logistic regression. For our main hypothesis of studying the impact of depression on the variation in postoperative functional status, multivariate linear regression analysis was performed, with adjustment for potential confounders. These were selected based on variables that resulted statistically significant on bivariate analysis or that were considered clinically relevant by the investigators. Significance was defined with a P value less than 0.05. Estimations were reported along with the corresponding 95%CI. Data was processed and statistical measures were performed with STATA v14 software (StataCorp, TX, United States).

This study was conducted respecting considerations related to the care of participants in clinical research, according to national and international guidelines, including those established in the Declaration of Helsinki.

RESULTS

From a total of 221 patients that were screened for eligibility, 90 patients were included for final analysis (Figure 1). The small loss in follow-up in this study involving elderly patients was justified by the inherent challenges of this population, such as mobility issues, health complications, and varying levels of engagement, which affected their ability to participate consistently. Out of 100 patients that were included in the general analysis, 22 (22%) screened positive for depression. Overall, mean patient age was 80 years ± 6.3 years, with an average of 77.6 years ± 6 years in the subgroup with depression and 80.6 years ± 6.3 years in the non-depressed group ($P = 0.05$). Other statistically significant differences found between both groups at baseline was that 16 (73%) patients in the depressed population had hypertension *vs* 70 (90%) in the opposite group ($P = 0.04$), and 2 (9%) had hypothyroidism in the depressed subset as opposed to 23 (29%) among the non-depressed, ($P = 0.06$).

Patients with depression had significantly greater cognitive impairment as assessed by the clock-face drawing test with respective medians of 5 (3-6) *vs* 6 (5-7), ($P = 0.06$), as well as more risk factors for confusional syndrome: Mean 8 ± 2 *vs* 6.5 ± 2.2, ($P = 0.006$). Depressed patients were found to be significantly more frail when assessed through both Edmonton: 15 (68%) *vs* 33 (42%), ($P = 0.05$), and Fried: 17 (77%) *vs* 42 (54%), ($P = 0.05$). Only 7 patients with depression (32%) were currently receiving antidepressant treatment. No statistically significant differences were found between the remaining baseline characteristics, including KSS preoperative scores, between both study groups. The results are shown in Table 1.

The mean postoperative Functional KSS in patients with depression was 65 ± 22.1 *vs* 66.3 ± 20.3 in the non-depressed population ($P = 0.8$). The mean KSS was 78.9 ± 10.4 and 78.4 ± 13.7, ($P = 0,9$), in patients with and without depression respectively. Mean variation between pre and postoperative Functional KSS was 33.8 (27.2) and 34.5 (22.7), ($P = 0,9$); and variation in KSS was 50.2 (19.5) and 44.9 (19.5), ($P = 0.28$), in depressed *vs* non-depressed patients. None of these differences showed statistical significance upon analysis (Table 2). No association was found between depression and variation in KSS after performing linear regression analysis. Spearman's rank correlation coefficient resulted in -0.0304 ($P = 0.8$) for Functional KSS variation and -0.1 ($P = 0.3$) for KSS variation.

Four patients (19%) presented major complications in the depressed group *vs* 16 (21%) among the non-depressed ($P = 0.82$). No significant differences were found upon individual analysis of each major complication (Table 3).

Multivariate logistic regression analysis was used to determine association between the independent variables (age, depression, frailty and high disease burden) and the combined event (death or major complication) at three months post surgery. Although none of these proved to be statistically significant, a statistical trend was described in association with age (Table 4). Finally, no statistically significant association was found between depression and length of hospital stay,

Table 1 Demographic characteristics of the population of depressed and non-depressed elderly adults that underwent total knee arthroplasty, *n* (%)

Characteristic	With depression (*n* = 22)	Without depression (*n* = 78)	*P* value
Female sex	14 (64)	51 (65)	0.9
Age (years)	77.6 ± 6	80.6 ± 6.3	0.05
Body mass index	31.4 ± 6.3	30.8 ± 4.7	0.6
Charlson index (IQR)	1 (0-1)	1 (0-2)	0.1
Diabetes	2 (9)	14 (18)	0.5
Hypertension	16 (73)	70 (90)	0.04
Hypothyroidism	2 (9)	23 (29)	0.06
Number of medications used	6.6 ± 3.5	7.6 ± 3.2	0.2
Older Americans Resources and Services Social Resource Scale (IQR)	1.5 (1-2)	1 (1-2)	0.3
Use of antidepressant medication	7 (32)	20 (26)	0.6
Use of Potentially Inappropriate Medication (Beers Criteria)	18 (82)	50 (64)	0.1
ADL (IQR)	4.5 (4-5)	5 (4-6)	0.2
Decreased ADL (< 6)	18 (82)	49 (63)	0.09
IADL (IQR)	6 (3-7)	6 (4-8)	0.3
Decreased IADL (< 6)	10 (45)	27 (35)	0.4
Clock-Drawing test (IQR)	5 (3-6)	6 (5-7)	0.06
Cognitive Impairment (Mini Mental score < 24 or Mini-Cog < 3)	6 (27)	27 (35)	0.5
Impaired gait speed test (more than 7 seconds per 4.5 meters)	15 (71)	47 (62)	0.5
Impaired chair stand test (greater than 15 seconds)	18 (95)	53 (79)	0.2
Risk factors for Confusional Syndrome	8 ± 2	6.5 ± 2.2	0.006
Edmonton Frail Scale	8 ± 2.5	5.8 ± 2.6	0.0006
Frailty according to Edmonton (≥ 7)	15 (68)	33 (42)	0.05
Fried Frailty Index	3.3 ± 1.2	2.5 ± 1.3	0.01
Frailty according to Fried (≥ 3)	17 (77)	42 (54)	0.05
Number of falls in the past year	12 (55)	28 (36)	0.1
Hand Grip (kg) (IQR)	18.5 (12-27)	19 (14-28)	0.5
Preoperative Knee KSS	27.4 ± 20.7	33.6 ± 16.5	0.2
Preoperative Functional KSS	31.8 ± 19.6	33.2 ± 21.2	0.8

ADL: Activities of daily living; IADL: Instrumental activities of daily living; IQR: Interquartile range; KSS: Knee Society Score.

readmission, number of physical therapy sessions or postoperative visits to the surgical team (Table 5).

DISCUSSION

The main finding of our study is that the presence of depression in elderly patients undergoing TKR does not seem to harm the postoperative functional status attained one year after surgery. This study allowed us to analyze our series of patients over 80 years old who suffer from depression and were treated with knee arthroplasty. It is the first registry to examine this phenomenon in the Latin American population. In addition to contributing to the understanding of our population, this work provides us with the opportunity to face new challenges in the treatment of these patients, enabling us to design intervention programs to address their depression from a multidisciplinary perspective. This is essential for improving their quality of life and facilitating their functional recovery. We acknowledge as a limitation of our work that the sample size could influence the validity of the findings and the implications this has for the applicability of the results to other populations. In the future, it will be necessary to conduct additional studies with larger and more diverse

Table 2 Variation between pre and postoperative functional status in patients with depression and without depression

Variable	Total (*n* = 90)	With depression (*n* = 21)	Without depression (*n* = 69)	*P* value
Postoperative Functional KSS	66 ± 20.6	65 ± 22.1	66.3 ± 20.3	0.8
Postoperative Knee KSS	78 ± 13	78.9 ± 10.4	78.4 ± 13.7	0.9
Delta Functional KSS	34.4 ± 23.7	33.8 ± 27.2	34.5 ± 22.7	0.9
Delta Knee KSS	46.1 ± 19.6	50.2 ± 19.5	44.9 ± 19.5	0.3

Values are expressed as means ± SD. KSS: Knee Society Score.

Table 3 Frequency of combined events (death or major complication) at 3 months postoperative in patients with and without depression, *n* (%)

Characteristic	With depression (*n* = 21)	Without depression (*n* = 75)	*P* value
Combined final event: Major complication or death.	4 (19)	16 (21.3)	1
Cerebrovascular accident (stroke)	1 (4.8)	0 (0)	N/A
Arrhythmia	0 (0)	1 (1.3)	N/A
Acute coronary event	0 (0)	1 (1.3)	N/A
Heart failure	0 (0)	5 (6.7)	N/A
Non-prosthetic infection	1 (4.8)	2 (2.7)	0.5
Periprosthetic infection	0 (0)	1 (1.3)	N/A
Acute renal failure	1 (4.8)	4 (5.3)	1
Major bleeding	0 (0)	2 (2.7)	N/A
Deep vein thrombosis/pulmonary embolism	1 (4.8)	5 (6.7)	1
Death	0 (0)	1 (1.3)	N/A

N/A: Not applicable.

Table 4 Association of depression, age, frailty and high disease burden with the combined final endpoint through multivariate logistic regression analysis

Independent variable	Odd ratio (95%CI)	*P* value
Depression	1.2 (0.3–4.8)	0.8
Age	1.1 (1–1.2)	0.06
Frailty (Fried Score ≥ 3)	1.7 (0.5-6)	0.4
High Disease Burden (Charlson ≥ 2)	1.3 (0.4–4.4)	0.7

samples to validate the results and improve the generalizability of the study.

There is significant controversy in the published literature regarding the influence of depression on outcomes after TKA. The reasons for these contradictory findings are unclear. They could be related to methodological issues of the varied study protocols such as the timing and type of test used to screen for depression, the instrument used to evaluate functional status during follow-up, or variations in sample size and baseline patient demographics. These controversies may be represented in the analysis of two articles that evaluated the influence of depression and other factors on postoperative outcomes of TKA. While Lee *et al*[19] conclude that the presence of night pain, neuropathic pain, or depressive disorders does not adversely affect outcomes after surgery, Vajapey *et al*[20] suggest that depression may have an adverse impact on joint arthroplasty outcomes.

Findings similar to ours have been published in previous studies. In 2013, Pérez-Prieto *et al*[21] described that patients with depression experienced significant improvement 12 months after surgery, and that this recovery was greater than that of non-depressed patients in several domains. They also reported that 86.8% of patients were no longer depressed one year after surgery[21]. Lingard and Riddle[22], did not specifically address depression in their study population, but assessed the impact of psychological distress, as measured by the Short Form 36 Health Survey mental health

Table 5 Comparison of other primary results among patients with and without depression, *n* (%)

Variable	With depression (*n* = 22)	Without depression (*n* = 78)	*P* value
Length of hospital stay	4.5 ± 1.9	4.6 ± 2.9	0.8
Readmission	2 (9)	8 (10)	1
Number of required sessions of physical therapy (IQR)	10 (10–10)	10 (10–10)	0.8
Number of consultations to the surgical team (IQR)	4 (3–4)	4 (3–4)	0.3

IQR: Interquartile range.

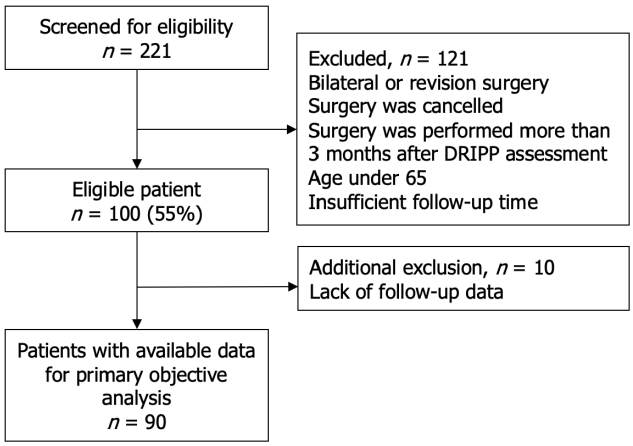


Figure 1 Flow diagram of the participants analyzed. DRIPP: Program Determination and Management of Risks for Practices and Procedures.

questionnaire, on postoperative outcomes. They found that the changes in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores for psychologically distressed patients were not significantly different from those for non-distressed patients. Nonetheless, a study published in 2007 that included 83 patients with a mean age of 66 years found that preoperative pain and depression were predictive of lower Functional KSS up to five years after surgery[23].

Cooper *et al*[4] screened patients for depressive disorder at baseline and a year after TKA and divided them into four groups: (1) Those who had no depressive disorder; (2) Those who had gained depression; (3) Those who had lost or resolved depression; and (4) Those who continued to maintain a depressive state. Depressed patients showed impaired recovery when measured by KSS and WOMAC scores.

The study highlights a concerning disconnect between the prevalence of cognitive impairment in depressed patients and the low treatment rates, suggesting a need for increased awareness and intervention strategies to address both mental health and cognitive functioning.

Other important aspects to take into consideration are the health costs and financial burden derived from associated comorbidities in patients undergoing TKA. Pugely *et al*[24] described the following factors that contribute to increased hospital costs and length of stay: (1) Inpatient death; (2) Ethnic minorities; (3) Recent weight loss; (4) Pulmonary-circulatory disorders; and (5) Hydroelectrolytic disturbances. Our research has proved that depressed patients do not have significantly increased healthcare resource requirements. In comparison with the non-depressed population, depressed patients did not present prolonged hospital stays, nor a greater number of physical therapy sessions or postoperative visits with the surgical team. One of the study's limitations is the small sample size. This is due in part to the fact that we only included patients who underwent surgery at a single site with a specific team. The other contributing factor was loss during follow-up. Several patients did not comply with the number of prespecified control visits and were thus excluded from the analysis. Nonetheless, our institution receives patient referrals from the whole country, which allows for a balanced population sample from a sanitary, social, and economic standpoint.

CONCLUSION

The presence of depression in patients with osteoarthritis should not be a limiting factor for surgical planning. The identification and treatment of depression before surgery may be an important strategy for the improvement of symptoms such as pain, reduction of the risk for acute confusional syndrome, cognitive impairment and subsequent development of frailty.

Elderly patients tend to accumulate multiple comorbidities and geriatric syndromes, which underscores the importance of integrated preoperative geriatric assessment. We believe that interdisciplinary work between geriatric specialists and surgical teams is vital in improving patient outcomes.

FOOTNOTES

Author contributions: Nicolino TI and Smietniansky M participated in the conception and design of the study and were involved in the acquisition, analysis, or interpretation of data; Boietti B, Garcia-Mansilla I, and Carbo L accessed and verified the study data; Martinez CB wrote the manuscript; all authors critically reviewed and provided final approval of the manuscript, were responsible for the decision to submit the manuscript for publication.

Institutional review board statement: The present study will be conducted in accordance with the ethical considerations for the care of participants in clinical research outlined in the Declaration of Helsinki and in compliance with the Guidelines for Research in Human Health (Resolution 1480/11) of the National Ministry of Health.

Informed consent statement: This is a retrospective study, meaning there is no risk to the patient, nor does it require the informed consent process. All information obtained from the electronic health records (EHR) will be used by the researchers with the strictest confidentiality, in accordance with the provisions of Law 25.326 on data protection. To ensure this, each patient will be assigned a consecutive number in a database accessible only to the principal investigator, which will be password-protected on a secured computer. Since the patients included in the study have already been discharged from follow-up and the nature of the study is observational and retrospective, with data collection exclusively from medical records—without requiring the active participation of patients or posing any harm to them or their healthcare coverage—informed consent will not be required for their inclusion in this study.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of atrial fibrillation in hospitalized patients undergoing endoscopic retrograde cholangiopancreatography: A nationwide analysis

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Abstract

BACKGROUND

Atrial fibrillation (AF) remains the most common cardiac arrhythmia. The safety of endoscopic retrograde cholangiopancreatography (ERCP) in patients with AF remains largely unknown.

AIM

To analyze the effect of AF on hospital outcomes in patients undergoing ERCP.

METHODS
We performed a retrospective cohort study using the Nationwide Inpatient Sample database. Adult patients with AF who underwent an inpatient ERCP were identified, then stratified by timing of ERCP, *via* international classification of diseases-10 codes. The primary outcome was all-cause in-hospital mortality. Secondary outcomes, including resource utilization, were assessed. Statistical analysis was performed using STATA software.

RESULTS
Of the 433245 patients that underwent an ERCP, 49615 had a diagnosis of AF. Patients with AF had a significantly higher in-hospital mortality compared to those without AF [3.82% *vs* 1.13%, odds ratio (OR) = 1.93, $P < 0.01$]. AF was significantly associated with increased hospital stay (+1.71 days), hospital charges ($21210), shock (OR = 2.17), sepsis (OR = 1.34), intensive care unit admission (OR = 2.41), acute kidney injury (OR = 1.51), as well as a decreased likelihood of discharge to home (OR = 0.59), (all with $P < 0.01$). These results were consistent after propensity score matching. Upon subgroup analysis, patients with AF, whom underwent ERCP > 72 hours, had worse outcomes including higher in-hospital mortality (adjusted OR = 1.47, $P < 0.01$).

CONCLUSION
By way of this large, national analysis it appears AF is associated with significantly worse hospitalization outcomes, inducing increased mortality, in those undergoing ERCP. Further prospective investigation is warranted to potentially guide clinical recommendations for patients with AF undergoing ERCP in this setting.

Key Words: Atrial fibrillation; Endoscopic retrograde cholangiopancreatography; Hospital outcomes; Length of stay; Nationwide Inpatient Sample

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Core Tip: Atrial fibrillation (AF) significantly worsens hospital outcomes, including increased mortality, longer hospital stays, higher costs, and complications, in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). Delaying ERCP beyond 72 hours in patients with AF further exacerbates these risks. Prospective studies are needed to optimize management strategies for this high-risk population.

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INTRODUCTION

Report on first endoscopic retrograde cholangiopancreatography (ERCP) was published in 1968[1]. With advancement in diagnostic imaging, the role of ERCP has been expanded to include both diagnostic and therapeutic domains. More than 50000 inpatient ERCP procedures are performed in the United States annually[2]. Common indications for ERCP include biliary pathologies (choledocholithiasis, benign and malignant stricture, sphincter of Oddi dysfunction), pancreatic diseases (recurrent acute pancreatitis, chronic pancreatitis, duct leaks, fluid collection, pancreatic cancer) [3].

Atrial fibrillation (AF) is the most common cardiac arrhythmia present in hospitalized patients, affecting nearly 1% of the United States population, and the prevalence is expected to increase 2.5-fold by 2050[4]. Patients with AF are usually on anticoagulants to reduce the risk of having a stroke—rendering it challenging to manage these patients when undergoing invasive medical procedures. As such, it can affect the decision on timing and planning of invasive procedures[5,6]. Patients with AF are also at increased risk of adverse outcomes including cardiovascular and ce-rebrovascular events[7-10]. However, there is lack of comprehensive studies on the impact of AF on ERCP outcomes, need for more specific data to guide clinical decisions. Our study is one of the largest studies from the Nationwide Inpatient Sample (NIS) database analyzing the association between AF and outcomes in patients undergoing ERCP. Since this study is based on a retrospective study from the NIS database and paves the way for future studies for analyzing causes on adverse outcomes in patients with AF to optimize outcomes. Given the large, nationwide sample size, findings are broadly applicable to hospitalized patients undergoing ERCP in the United States.

Data regarding the outcomes of patients with AF undergoing ERCP remains limited. Herein, we sought to analyze the effect AF has on hospitalization outcomes in patients undergoing ERCP.

MATERIALS AND METHODS

Data source

In this retrospective cohort study, we used the Healthcare Cost and Utilization Project NIS database. NIS is the largest publicly available all-payer inpatient database in the United States. The NIS database contains data from 14.1 million hospital stays[8]. It contains de-identified clinical and nonclinical elements at both the patient-level and hospital-level. Institutional Review Board approval was not required for this study as it was performed using de-identified and publicly available data.

Inclusion and exclusion criteria

The inclusion criteria comprised all patients who underwent ERCP during hospitalization, totaling 429400 patients. Patients younger than 18 years were excluded. The total number of patients included in the study was 423245, divided into two groups: (1) 49018 patients with AF; and (2) 374227 patients without.

Study population

We used international classification of diseases (ICD)-10-CM codes (l48, l48.1, l48.2, l48.91) to identify all adult (> 18 years old) patients with a primary or secondary diagnosis of AF, who underwent an ERCP (ICD-10: BF111ZZ) during hospitalization. We stratified this population according to the timing of ERCP: (1) ERCP within 24 hours of admission; (2) ERCP between 24-48 hours of admission; (3) ERCP between 48-72 hours of admission; and (4) ERCP after 72 hours of admission. Inclusion and exclusion criteria are shown in a flow diagram (Figure 1).

Study variables

Patient and hospital level demographics collected included: (1) Age; (2) Sex; (3) Race; (4) Median household income; (5) Insurance; (6) Hospital bed size; (7) Hospital teaching status; (8) Hospital region; and (9) Hospital location. Burden of comorbidities was assessed using Charlson comorbidity index.

Primary and secondary outcomes

The primary outcome was all-cause in-hospital mortality. Secondary outcomes were: (1) Mean length of stay (LOS); (2) Mean hospitalization charges; (3) Costs mean time to ERCP; (4) Incidence of shock; (5) Incidence of sepsis; (6) Incidence of acute kidney injury (AKI); (7) Incidence of intensive care unit (ICU) admission; (8) Incidence of blood transfusion; and (9) Likelihood of discharge to home.

Statistical analysis

Statistical analyses were performed using STATA, version 16.0 (StataCorp., College Station, Texas, United States). Univariate screen was initially performed to calculate unadjusted odds ratio (OR) and a multivariate logistic regression model to calculate adjusted OR (aOR). Logistic regression was used for binary outcomes and linear regression was used for continuous outcomes. Proportions were compared using the Fisher exact test and continuous variables were compared using the Student *t*-test. Propensity score matching (PSM) with 1:1 matching was also performed on unweighted sample to match the patients with AF to patients without AF and adjust for confounders. Adequacy of propensity matching was assessed by checking the balancing property of the propensity score before the analysis. A P value < 0.05 was considered statistically significant for all outcomes.

RESULTS

Patient and hospital characteristics

A total of 433245 adult patients underwent ERCP and 49615 (11.45%) had a diagnosis of AF. Mean age was 59.9 years, and majority of patients were female (57.44%) and white (66.98%). Medicare was the primary payer insurance (48.3%) and

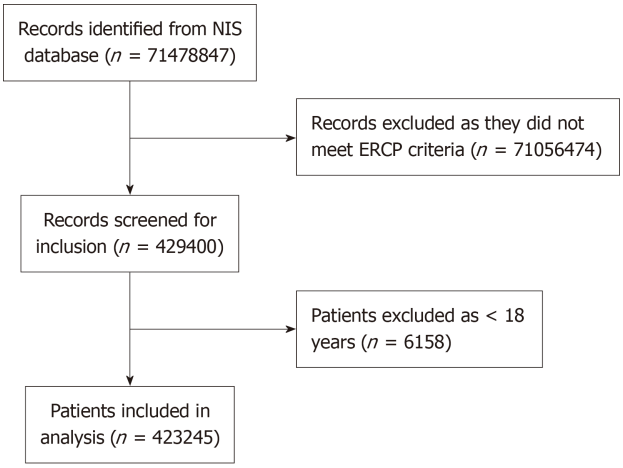


Figure 1 Inclusion flow diagram. ERCP: Endoscopic retrograde cholangiopancreatography; NIS: Nationwide Inpatient Sample.

patients were predominantly admitted to teaching hospitals (71.84%) (Tables 1 and 2).

Most common reasons for ERCP

The most common primary diagnosis was "sepsis (unspecified organism)" (6.6%). This was followed by "obstruction of bile duct" (5.02%), "calculus of bile duct without cholangitis or cholecystitis without obstruction" (4.31%), "calculus of bile duct without cholangitis or cholecystitis with obstruction" (3.43%) and "biliary acute pancreatitis" (2.97%) (Table 3).

All cause in-hospital mortality

Total all cause in-hospital mortality was 1.44% (6245 out of 433245 patients). The total mortality was higher in patients with AF (1895 patients) compared to patients without AF (4350 patients) (3.82% *vs* 1.13%). There was a significant difference in all cause in-hospital mortality between patients with AF compared to patients without AF [aOR = 1.93, (95%CI: 1.68-2.22), $P < 0.01$].

Mean time to ERCP

The mean time to ERCP in all the study population was 2.22 days. In patients with AF, the mean time to ERCP was 2.94 days and in patients without AF, it was 2.13 days. Patients with AF had a significantly longer mean time to ERCP. The mean adjusted difference was 0.8 days (95%CI: 0.72-0.89, $P < 0.01$).

Mean LOS

The overall mean LOS was 5.92 days for all patients undergoing ERCP. Mean LOS was 5.63 days (95%CI: 5.57-5.70) in patients without AF and 8.12 days (95%CI: 7.95-8.29) in patients with AF. Patients with AF had significantly longer mean LOS compared to patients who did not have AF (+1.71 days, $P < 0.01$).

Mean hospitalization charges and costs

The mean hospitalization charges and cost for patients undergoing ERCP was $82950 and $19939 respectively. There was a significant difference in mean hospitalization charges [$+21210 (95%CI: $18370-$24048, $P < 0.01$)], and in mean hospitalization costs [$+4869 (95%CI: $4183-$5556, $P < 0.01$)] between those with and without AF.

Shock

The overall incidence of shock was 4.06% in patients undergoing ERCP. The incidence of shock in patients with AF was 10.27% and in patients without AF was 3.26%. There was a significant difference in the likelihood of shock in patients who had AF compared to patients without AF (aOR = 2.17, 95%CI: 1.98-2.38, $P < 0.01$).

Sepsis

Out of the 433245 patients undergoing ERCP, 15880 (3.66%) patients were diagnosed with sepsis during the hospital stay. Patients with AF had 6.30% incidence of sepsis compared to 3.32% in patients without AF. There was a significant difference in the likelihood of sepsis between patients who had AF compared to patients without AF (aOR = 1.34, 95%CI: 1.21-1.48, $P < 0.01$).

AKI

The overall incidence of AKI in patients undergoing ERCP was 63370 (14.62%). Patients with AF had 29.47% incidence of AKI compared to 12.7% in patients without AF. There was a significant difference in the likelihood of AKI between patients who had AF compared to patients without AF (aOR = 1.51, 95%CI: 1.43-1.60, $P < 0.01$).

Table 1 Characteristics of patients undergoing endoscopic retrograde cholangiopancreatography in hospital, *n* (%)

Variable	
Total study population	433245
Female	248856 (57.44)
Mean age in years	59.9
Insurance provider	
Medicare	209257 (48.30)
Medicaid	66200 (15.28)
Private	134912 (31.14)
Uninsured	22876 (5.28)
Charlson comorbidity index	
0	168749 (38.95)
1	89378 (20.63)
2	56148 (12.96)
3 or more	118970 (27.46)
Median income in patient zip code	
$1–$38999	121611 (28.07)
$39000–$47999	114680 (26.47)
$48000–$62999	107401 (24.79)
$63000	89553 (20.67)
Hospital region	
Northwest	74864 (17.28)
Midwest	96180 (22.20)
South	164806 (38.04)
West	97395 (22.48)
Hospital location	
Rural	20276 (4.68)
Urban	412969 (95.32)
Hospital size	
Small	67586 (15.60)
Medium	119965 (27.69)
Large	245694 (56.71)
Teaching hospital	311243 (71.84)
Race	
White	290187 (66.98)
Black	41071 (9.48)
Hispanic	67759 (15.64)
Asian or Pacific Islander	16203 (3.74)
Native American	3555 (0.82)
Other	14470 (3.34)
Weekend admission	102235 (23.60)

Table 2 Characteristics of patients undergoing endoscopic retrograde cholangiopancreatogram in hospital: Atrial fibrillation *vs* no-atrial fibrillation, *n* (%)

Variable	With AF: 49615	Without AF: 383630	*P* value
Female	22475 (45.30)	226380 (59.01)	< 0.01
Mean age in years	76.40	57.70	< 0.01
Insurance provider			< 0.01
Medicare	41910 (84.47)	167032 (43.54)	
Medicaid	1677 (3.38)	64641 (16.85)	
Private	5596 (11.28)	129475 (33.75)	
Uninsured	432 (0.87)	22482 (5.86)	
Charlson comorbidity index			< 0.01
0	7482 (15.08)	161239 (42.03)	
1	9015 (18.17)	80370 (20.95)	
2	9104 (18.35)	47071 (12.27)	
3 or more	24014 (48.40)	94950 (24.75)	
Median income in patient zip code			< 0.01
$1–$38999	11987 (24.16)	109603 (28.57)	
$39000–$47999	13639 (27.49)	101048 (26.34)	
$48000–$62999	12503 (25.2)	94910 (24.74)	
$63000	11486 (23.15)	78069 (20.35)	
Hospital region			< 0.01
Northwest	10141 (20.44)	64718 (16.87)	
Midwest	11958 (24.10)	84206 (21.95)	
South	17494 (35.26)	147314 (38.40)	
West	10022 (20.20)	87392 (22.78)	
Hospital location			0.05
Rural	2128 (4.29)	18145 (4.73)	
Urban	47487 (95.71)	365485 (95.27)	
Hospital size			< 0.05
Small	7124 (14.36)	59424 (15.49)	
Medium	13922 (28.06)	106073 (27.65)	
Large	28569 (57.58)	218133 (56.86)	
Teaching hospital	35772 (72.10)	275446 (71.80)	0.59
Race			< 0.01
White	41309 (83.26)	249282 (64.98)	
Black	2575 (5.19)	38516 (10.04)	
Hispanic	2789 (5.62)	64526 (16.82)	
Asian or Pacific Islander	1567 (3.16)	14654 (3.82)	
Native American	264 (0.53)	3302 (0.86)	
Other	1111 (2.24)	13350 (3.48)	
Weekend admission	11932 (24.05)	90306 (23.54)	0.27

AF: Atrial fibrillation.

Table 3 Top 5 most common primary diagnosis in patients undergoing endoscopic retrograde cholangiopancreatogram

Serial number	Diagnosis
1	Sepsis, unspecified organism
2	Obstruction of bile duct
3	Calculus of bile duct without cholangitis or cholecystitis without obstruction
4	Calculus of bile duct without cholangitis or cholecystitis with obstruction
5	Biliary acute pancreatitis

ICU admission

The total incidence of ICU admission in patients undergoing ERCP was 12470 (2.87%). There was a significant difference in likelihood of ICU admission in patients who had AF compared to patients who did not have AF (7.27% *vs* 2.30%, aOR = 2.41, 95%CI: 2.16-2.69, $P < 0.01$).

Blood transfusion

Overall, 1365 (0.31%) patients undergoing ERCP needed blood transfusion. The rate of blood transfusion in patients with AF was 0.49% and in patients without AF was 0.29%. On multivariate analysis, there was no significant difference in blood transfusion in these groups (aOR = 1.37, 95%CI: 0.96-1.96, $P = 0.08$).

Home discharge

A total of 323985 (74.78%) patients undergoing ERCP were discharged home after the hospitalization. Total 78.2% patients without AF were discharged home compared to 48.34% patients with AF. There was a significant difference in likelihood of discharge to home in patients who had AF compared to patients who did not have AF (aOR = 0.59, 95%CI: 0.56-0.62, $P < 0.01$).

Propensity score matched analysis

The results of the PSM outcome analysis are presented in Table 4. The results after PSM were consistent with results from multivariate regression analysis. Patients with AF had higher mortality rate (aOR = 3.29, $P < 0.01$), longer mean LOS (adjusted coefficient: +1.56 days, $P < 0.01$), longer time to ERCP (adjusted coefficient: +0.5 days, $P < 0.01$) and higher mean hospitalization charges (adjusted coefficient: $17972, $P < 0.01$). There was no difference in likelihood of blood transfusion between the two groups (aOR = 1.15, $P = 0.57$).

Subgroup analysis

The outcomes of subgroup analysis based on timing of ERCP are summarized in Table 5. Compared to ERCP within the first 24 hours of admission, there was no significant difference in mortality in patients getting ERCP after 24 hours but within 72 hours (aOR = 0.712, 95%CI: 0.50-1.00, $P = 0.0576$; aOR = 0.86, 95%CI: 0.59-1.25 $P = 0.43$) respectively. Delaying ERCP to more than 72 hours increased the odds of mortality significantly (aOR = 1.46, 95%CI: 1.23-1.74, $P < 0.06$). The total hospitalization charges and costs were significantly increased when ERCP was delayed by more than 48 hours from admission. Patients who underwent ERCP after 72 hours had an additional $69150 ($P < 0.01$) and $16933 ($P < 0.01$) added to their total hospitalization charges and cost respectively.

Performing ERCP after 24 hours but within 72 hours decreased the risk of shock in patients with AF (aOR = 0.65, 95%CI: 0.53-0.81, $P < 0.01$ and aOR = 0.60, 95%CI: 0.47-0.78, $P < 0.01$) respectively. ERCP after 72 hours increased the likelihood of shock (aOR = 1.30, 95%CI: 1.12-1.52, $P < 0.01$). Similar trend was observed for ICU admission as well. Patients with ERCP 24-48 hours of admission and 48-72 hours of admission had lower odds of ICU admission (aOR = 0.57, 95%CI: 0.43-0.75, $P < 0.01$ and aOR = 0.70, 95%CI: 0.52-0.94, $P < 0.01$) respectively. Delaying ERCP to more than 72 hours from admission resulted in increased odds of ICU admission (aOR = 1.46, 95%CI: 1.23-1.74, $P < 0.06$). Similarly, performing ERCP 48-72 hours of admission resulted in decreased odds of sepsis (aOR = 0.72, 95%CI: 0.54-0.97, $P < 0.05$). Patients with ERCP after 72 hours also had increased likelihood of AKI (aOR = 1.72, 95%CI: 1.53-1.92, $P < 0.01$). Patients with ERCP performed between 48-72 hours and after 72 hours were less likely to be discharged home (aOR = 0.85, 95%CI: 0.74-0.98, $P < 0.01$ and aOR = 0.48, 95%CI: 0.43-0.43, $P < 0.01$) respectively (Table 5).

DISCUSSION

To our knowledge, this is the first nationwide study examining the impact of AF in hospitalized patients undergoing ERCP. Our study highlights that AF predisposes one to significantly increased in-hospital mortality rates, increased LOS, longer time to ERCP, and higher total hospitalization cost and charges.

We hypothesize that risk of increased in-hospital mortality is attributed to a combination of patients' clinical comorbidities and medication use–namely anticoagulants. Pilgrim et.al observed that in patients with coronary artery disease undergoing revascularization with drug eluting stents, AF increased the risk of all-cause mortality (hazard ratio =

Table 4 Outcomes in patients undergoing endoscopic retrograde cholangiopancreatogram: Atrial fibrillation *vs* no-atrial fibrillation

Study population with ERCP (*n* = 433245)						
	Outcomes	**Without AF**	**With AF (multivariate regression)**	***P* value**	**With AF (after propensity matching)**	***P* value**
1	In-hospital mortality	1.13%	3.82%			
	OR	Ref	3.46	< 0.01	3.29	< 0.01
	AOR	Ref	1.93	< 0.01	1.74	< 0.01
2	Mean time to ERCP (days)	2.13	2.94		2.97	
	Adjusted coefficient	Ref	+0.8	< 0.01	+0.50	< 0.01
3	Mean length of stay (days)	5.6	8.12			
	Adjusted coefficient	Ref	+1.71	< 0.01	+1.56	< 0.01
4	Mean total charge ($)	79963	106017		100359	
	Adjusted coefficient ($)	Ref	21209	< 0.01	17972	< 0.01
5	Mean total cost ($)	19214	25534			
	Adjusted coefficient ($)	Ref	4869	< 0.01	Not applicable	
6	Shock	3.26%	10.27%			
	OR	Ref	3.39	< 0.01	3.24	< 0.01
	AOR	Ref	2.17	< 0.01	2.04	< 0.01
7	Sepsis	3.32%	6.30%			
	OR	Ref	1.95	< 0.01	1.96	< 0.01
	AOR	Ref	1.34	< 0.01	1.30	< 0.01
8	Intensive care unit admission	2.30%	7.27%			
	OR	Ref	3.31	< 0.01	3.08	< 0.01
	AOR	Ref	2.41	< 0.01	2.31	< 0.01
9	Acute kidney injury	12.7%	29.47%			
	OR	Ref	2.87	< 0.01	2.76	< 0.01
	AOR	Ref	1.51	< 0.01	1.42	< 0.01
10	Blood transfusion	0.29%	0.49%			
	OR	Ref	1.69	< 0.01	1.67	< 0.05
	AOR	Ref	1.37	0.08	1.15	0.57
11	Home discharge	78.2%	48.34%			
	OR	Ref	0.26	< 0.01	0.27	< 0.01
	AOR	Ref	0.59	< 0.01	0.62	< 0.01

AF: Atrial fibrillation; AOR: Adjusted odds ratio; ERCP: Endoscopic retrograde cholangiopancreatogram; *N*: Total number of patients; OR: Odds ratio; Ref: Reference.

1.67, $P < 0.003$)[11]. Another study noticed higher in-hospital mortality in patients with stroke and AF (12.1% *vs* 6.5%)[12]. These studies highlight the negative impact of AF on in-hospital outcomes of patients. This is consistent with the findings in our study and indicates that invasive procedures are likely riskier in patients with AF[13]. Additionally, in our study, almost 30% of patients with AF undergoing ERCP were found to have AKI, and patients with AF had 50% higher odds of developing AKI. We postulate that these additional comorbidities probably account for the increase in LOS and resource utilization in patients with AF.

With use of anticoagulants for stroke prevention in AF, timing of ERCP can get challenging[14]. A key finding of our study is that delayed ERCP (> 72 hours) had increased odds of mortality compared to ERCP < 24 hours of admission. Similar findings have been previously reported by Mulki *et al*[15] in which they compared outcomes of early *vs* delayed ERCP in patients with acute cholangitis. In contrast, our study demonstrated that in patients with AF, performing ERCP

Table 5 Outcomes in patients with atrial fibrillation undergoing endoscopic retrograde cholangiopancreatogram 0-24 hours *vs* 24-48 hours *vs* 48-72 hours *vs* > 72 hours, *n* (%)

Patients getting ERCP with AF (*n* = 49615)								
	Outcomes	ERCP 0-24 hours	ERCP 24-48 hours	*P* value	ERCP 48-72 hours	*P* value	ERCP > 72 hours	*P* value
		19900 (40.10)	9005 (18.14)		6180 (12.45)		14530 (29.28)	
1	In-hospital mortality	3.46%	2.55%		3.07%		5.4%	
	OR	Ref	0.72	0.06	0.88	0.50	1.58	< 0.01
	AOR	Ref	0.71	0.05	0.86	0.43	1.47	< 0.01
2	Mean length of stay							
	Adjusted coefficient(days)	Ref	0.65	< 0.01	1.74	< 0.01	6.5	< 0.01
3	Mean total charge ($)							
	Adjusted coefficient ($)	Ref	1918	0.45	11861	< 0.01	69150	< 0.01
4	Mean total cost							
	Adjusted coefficient ($)	Ref	197	0.68	2628	< 0.01	16933	< 0.01
5	Shock	10.42%	7.27%		6.71%		13.45%	
	OR	Ref	0.67	< 0.01	0.61	< 0.01	1.33	< 0.01
	AOR	Ref	0.65	< 0.01	0.60	< 0.01	1.30	< 0.01
6	Sepsis	6.80%	5.49%		5.17%		6.60%	
	OR	Ref	0.76	0.6	0.74	< 0.05	0.96	0.74
	AOR	Ref	0.8	0.07	0.72	< 0.05	0.99	0.90
7	Intensive care unit admission	7.01%	4.27%		5.01%		10.46%	
	OR	Ref	0.59	< 0.01	0.70	< 0.01	1.54	< 0.01
	AOR	Ref	0.57	< 0.01	0.70	< 0.01	1.46	< 0.01
8	Acute kidney injury	25.12%	25.76%		28.72%		38.05%	
	OR	Ref	1.03	0.6	1.20	< 0.05	1.8	< 0.01
	AOR	Ref	0.98	0.8	1.13	0.11	1.72	< 0.01
9	Blood transfusion	0.5%	0.16%		0.24%		0.72%	
	OR	Ref	0.30	0.05	0.43	0.18	1.30	0.39
	AOR	Ref	0.20	< 0.01	0.44	0.19	1.04	0.89
10	Home discharge	56.39%	55.10%		50.54%		39.26%	
	OR	Ref	0.94	0.36	0.79	< 0.01	0.49	< 0.01
	AOR	Ref	0.99	0.97	0.85	< 0.05	0.48	< 0.01

AF: Atrial fibrillation; AOR: Adjusted odds ratio; ERCP: Endoscopic retrograde cholangiopancreatogram; *N*: Total number of patients; OR: Odds ratio; Ref: Reference.

within 24-48 hours resulted in shorter LOS compared to ERCP within 24 hours. Likewise, performing ERCP after 24 hours but within 72 hours resulted in decreased incidence of shock, sepsis and ICU admission[16]. Delaying ERCP until after 24 hours of admission leads to improved resuscitation efforts with intravenous fluids and antibiotics in patients needing ERCP[17], and this is likely the reason for our observation.

Furthermore, ERCP after 72 hours of admission had consistently poor outcomes when compared to ERCP within 24 hours of admission. These patients had higher in-hospital mortality, longer LOS, increased shock, increased AKI, increased ICU admission and reduced likelihood of home discharge. This is uniform with most of the studies and guideline recommendation of ERCP within 72 hours in patients without cholangitis[17-20]. Our study is constrained by its retrospective nature and utilization of billing database. Nevertheless, the revelations in our study warrant prospective studies to determine the optimum timing of ERCP in patients with AF, to solidify the gap of uncertainty among physicians.

Although our results are robust, several limitations within the study must be considered. First, this is a database study that heavily relies on accurate coding of all inpatient and procedure codes. We have to accept that there may be instances of underreporting or selective reporting. Second, ERCP is an invasive procedure and certain amount of selection bias naturally exists. The NIS does not contain important clinical information such as laboratory and imaging data. These are often used to determine the necessity and urgency of procedures and to predict outcomes[21,22]. Despite such limitations, our study has numerous strengths. The largest strength is the fact that we included a large sample size (> 300000 patients) providing an accurate representation of the entire United States population. We used multivariate regression analysis and PSM to account for potential confounders. PSM helps to design observational studies to mimic randomized experiments to produce unbiased treatment effects[23]. In the absence of any relevant study looking at the effect of AF on ERCP, our study was able to analyze various outcomes not reported in the literature yet. Furthermore, we also stratified patients based on the timing of ERCP giving an additional perspective to the analysis of outcomes in patients with or without AF. Our large sample size from the NIS database could well be a generalized representation of the United States population

CONCLUSION

Our study demonstrates that AF is associated with significantly worse hospital outcomes in patients undergoing ERCP, including increased in-hospital mortality, longer LOS, delayed ERCP timing, and higher healthcare costs. These findings emphasize the complexity of managing patients with AF in the setting of invasive procedures, likely influenced by comorbidities, anticoagulation use, and procedural risks.

Clinically, these results highlight the importance of optimizing perioperative management in patients with AF undergoing ERCP. Careful risk stratification, anticoagulation management, and timely intervention are crucial to improving outcomes. Our study suggests that performing ERCP between 24-72 hours after admission may reduce the risk of sepsis, shock, ICU admission, and mortality, reinforcing the need for individualized procedural timing in this high-risk population.

Despite the robust nature of our analysis, our study is limited by its retrospective design and reliance on administrative coding. Future prospective studies are necessary to validate these findings, explore the mechanisms underlying poor outcomes in AF patients undergoing ERCP, and determine the optimal timing of intervention. Establishing evidence-based guidelines tailored to this subgroup of patients will be essential in improving patient outcomes and guiding clinical decision-making.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Preoperative marking of the proximal resection margin in esophageal cancer with a surgical fiducial marker: First experiences

Trygve U Solstad, Andreas W Mucha, August A Olsen, Hanne Grossjohann, Michael P Achiam

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Abstract

BACKGROUND

Neoadjuvant therapy can reduce the size of gastroesophageal tumors to the extent that they are no longer macroscopically visible. This may increase the risk of microscopic-positive resection margins. One potential method to reduce this uncertainty could be the preoperative endoscopic marking of proximal tumor margins with BioXmark®, a novel liquid fiducial marker. This study aimed to report the initial experiences of the first ten patients marked with BioXmark®.

AIM

To evaluate the visibility of BioXmark® on ultrasound after preoperative marking of the proximal resection line of an esophageal tumor.

METHODS

The circumference of the esophagus was endoscopically marked preoperatively with a fiducial marker in four quadrants, 5 cm proximal to the tumor. During the surgery, the surgeon's proposed proximal resection line was marked. Next, an ultrasound probe was used to identify the previously placed fiducial markers, and its placement was marked. The difference between the surgeon's proposed resection line and the fiducial marker was measured intraoperatively and subsequently examined with respect to the resection margin and status.

RESULTS

BioXmark® was implanted in ten patients, 5 cm proximal to the tumor. The surgeon's proposed resection line was positioned 2-6 cm proximally to the surgical marker line. Technical success of injecting the fiducial marker was achieved in all ten patients. In six patients, the marker was successfully identified

intraoperatively on ultrasound. No peri- or postoperative adverse events related to BioXmark® implantation were found.

CONCLUSION
Excellent technical success with the implantation of the fiducial surgical marker was achieved, but limited intraoperative visibility on ultrasound was achieved. Further studies are required to optimize its clinical application.

Key Words: BioXmark®; Gastroesophageal junction cancer; Gastroesophageal surgery; Surgical oncology; Fiducial marker

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Core Tip: This study explores the use of the liquid fiducial marker BioXmark® to enhance precision in cancer surgery. BioXmark® was injected 5 cm proximal to the tumor duringpreoperative nasal gastroscopy. The injected BioXmark® was subsequently identified *in vivo* using perioperative ultrasound. By improving intraoperative visualization of tumor margins, fiducial markers may increase resection precision and the likelihood of achieving an R0 resection, potentially reducing patient morbidity and mortality. The marker's technical feasibility and safety were demonstrated, although further studies are required to optimize its visibility and clinical application.

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INTRODUCTION

Gastroesophageal cancer is one of the leading causes of cancer-related deaths worldwide, and its prevalence is increasing [1,2]. In Denmark, approximately 900 people are diagnosed annually, the majority of tumors being gastroesophageal junction adenocarcinomas (GEJ AC)[3]. The Danish national guidelines for the surgical treatment of GEJ AC is an R0 resection with a proximal resection margin at least 5 cm from the tumor, measured *in vivo*[4]. These recommendations are based on a large study that showed a significantly increased survival in patients with a proximal resection margin larger than 3.8 cm compared to those with a resection margin less than 3.8 cm[5]. This survival difference was identified only by observing patients who had received an R0 resection. Neoadjuvant chemotherapy often leads to tumor shrinkage, which may be so significant that the tumor is no longer macroscopically visible. Thus, the surgeon must digitally palpate the area where the tumor has been described, and measure and set the resection margin with an educated estimate. However, no studies have confirmed whether this subjective method achieves the recommended 5 cm margins. Precise tumor location is essential to achieve an R0 resection while ensuring optimal perfusion, and the current methods to achieve this are prone to error.

At Copenhagen University Hospital Rigshospitalet, we introduced a liquid fiducial marker to mark the proximal resection line 5 cm proximal to the tumor *in vivo*. The liquid fiducial marker was implanted during preoperative gastroscopy to ensure an acceptable resection margin. BioXmark® (Nanovi A/S, Lyngby, Denmark) is a liquid injectable and adherent fiducial marker used for radiographic marking of soft tissue. BioXmark® has shown promising results in image-guided adaptive radiotherapy for cancers of the lungs, bladder, rectum, and esophagus[6-10].

This study aimed to collect real-world data from the first ten patients in whom BioXmark® was used to preoperatively mark the proximal resection margin of GEJ tumors. To our knowledge, this is the first study on this application.

MATERIALS AND METHODS

Study design

This was a quality assurance study on prospectively collected data from the first ten consecutive patients undergoing esophageal resection for GEJ tumors with tumor margins marked by BioXmark®. This study was conducted at a single Danish tertiary referral center for upper gastrointestinal malignancies, covering a population of 2.8 million inhabitants. As BioXmark® was implemented as a standard supplement to the standard operating procedure for esophagectomies at Rigshospitalet at the time and the present study was a quality assurance study, ethical committee approval was not required, no inclusion and exclusion criteria were determined, and no control group was included. At the time of referral to Rigshospitalet, all patients were asked to sign a consent form to review their data and health information for quality control. This study was approved as a quality assurance project by the hospital manager, The Danish Data Protection Agency (P-2021-800), and the Regional Committee for the Capital Region in Denmark (H-21041919). This study was registered at ClinicalTrials.gov (ID: NCT05069766).

Outcomes

The primary outcome of this study was to describe our experience using a liquid fiducial marker to preoperatively mark the proximal resection line of the tumor margin in patients with GEJ tumors. Moreover, we aimed to describe the performance of BioXmark® in terms of visibility during surgery using ultrasound. The secondary outcome was to confirm the safety of BioXmark when used according to the label regarding adverse events related to implantation.

Data collection and variables

Clinical patient data and information about BioXmark® implantation and subsequent operation were retrieved from electronic health records (Sundhedsplatformen, Epic Systems Corporation, Verona, Wisconsin, United States). Patient records were evaluated by Andreas W Mucha and Trygve U Solstad, and unclear cases were discussed with August A Olsen and Michael P Achiam. Electronic patient records were individually reviewed, and information collected included age, sex, American Society of Anesthesiologists score, information regarding preoperative endoscopy examinations (tumor location, tumor distance from incisors), information about neoadjuvant treatment, and histological tumor type. Statistical analysis in this study was primarily descriptive, using means, standard deviations, and percentages to summarize the data.

Fiducial marker

BioXmark consists of iodinated sucrose acetate isobutyrate and sucrose acetate isobutyrate mixed with ethanol. After implantation, ethanol diffuses out of the marker and into the surrounding tissue, where it is metabolized, thus increasing marker viscosity. This results in a highly viscous and sticky gel-like marker[11]. BioXmark® can be implanted with standard endoscopic equipment and will form sticky and soft markers *in vivo* that are adaptive to the surrounding tissue. Owing to the proprietary iodine-based contrast agent, the marker is visible on numerous imaging modalities, including X-ray, ultrasound, and magnetic resonance imaging (MRI)[11].

Placement of the fiducial marker: Three upper gastrointestinal surgery specialists individually placed the fiducial marker in ten patients. The location of the GEJ tumor was preoperatively described in cm from the incisors as seen on the centimeter marking on the scope at an index gastroscopy. After induction, the specialist performed a nasal gastroscopy. The tumor was endoscopically identified based on the aforementioned preoperative measurements, and the scope was retracted 5 cm proximal to the tumor. Any segment of Barrett's dysplasia or otherwise pathologic finding was considered, and the border of injection was moved accordingly. An injection of 1–2 mL isotonic saline was placed in the submucosal layer of the esophagus in four quadrants using a standard 10 mL syringe of isotonic saline and a 4 mm Novaject injection needle (Vytil, Bagnolet, France). Next, the saline syringe was switched to a 5 mL standard plastic syringe filled with 1 mL BioXmark®, which was used to fill the dead space of the injection needle. Subsequently, another vial of 1 mL BioXmark® was filled into a 1 mL Luer Lock micro-dosing syringe (Vlow Medical, JC Eindhoven, The Netherlands). The needle was retracted into the lumen, and the remaining isotonic saline was flushed into the lumen. At the visual cue of viscous liquid emerging from the tip of the injection needle inside the lumen, 60–100 µL of the fiducial marker was injected into each of the four submucosal saline deposits. A minimum volume of 60 µL per depot was recommended by the manufacturer. To ensure that a satisfactory depot was placed, defined as a clear visual bulge after injection, the amount of the fiducial marker required was adjusted on a case-by-case basis by the operating consultant surgeon. Finally, the injection needle and nasal scope were retracted, a nasogastric tube was placed, and standard hybrid robot-assisted or open Ivor-Lewis esophagectomy was performed.

Surgical procedure: A standard Ivor-Lewis esophagectomy technique, either as a hybrid or as an open procedure, was performed for each patient. The operation was initiated with the abdominal part, either open or robotic-assisted, and subsequently, a right thoracotomy was performed in all cases. Subtotal esophagectomy was performed with gastric pull-up and stapled gastroesophageal anastomosis. Lymphadenectomy was performed 2-field with D2 resection in the abdomen, dissection of the truncal celiac nodes, and *en-bloc* mediastinal lymphadenectomy. Paraesophageal and subcarinal lymph nodes were also removed, but cervical lymphadenectomy was not performed[12]. The patients received anesthetic management according to standard clinical practice.

Locating BioXmark® and measuring distance to the tumor: Before esophageal transection, the surgeon marked the proposed proximal resection line using a sterile pen. This estimation was based on the macroscopic evaluation of tumor extension, digital palpation of the area, and guidelines stating that the resection must be placed at least 5 cm proximal to the tumor. Next, using a TE7 Portable Ultrasound System (Mindray Medical International Limited, Shenzhen, Guangdong, China) with a T-probe and sterile draping, the exterior of the esophagus was scanned *in vivo*. If the BioXmark® was identified, a sterile marker was used to mark the area. The distance from the surgeon's proposed resection line to the fiducial marker was measured. Resection was performed on the proposed resection line determined by the surgeon. The resected specimen from all ten patients was transported to a nearby sterile table and scanned *ex vivo* using an ultrasound probe. The exterior of the esophagus was scanned first; then, the resected esophagus was cut with scissors, and the lumen was scanned. If the fiducial marker could not be identified through ultrasound by the surgeon, the operation was continued as planned, with the surgeon performing the resection as originally proposed.

RESULTS

A total of ten patients with GEJ tumors undergoing open or robotic Ivor Lewis esophagectomy were included in the period from February 2022 to August 2022. The baseline characteristics of the patients are shown in Table 1. All ten patients received an R0 resection at the proximal border, with eight cases identified as adenocarcinomas, one mixed neuroendocrine non-neuroendocrine neoplasm, and one mucoepidermoid carcinoma. Seven tumors were palpable *in vivo*, with a mean tumor size of 32.7 mm. The mean microscopic distance to the proximal tumor resection line was 37.3 mm, while the mean macroscopic distance was 45.3 mm, respectively. Barrett's dysplasia was present in two out of ten resected specimens. Table 2 provides detailed histopathology and surgical procedure specifications.

Placement of BioXmark®

The mean distance from the incisors to the proximal tumor border was 39.3 cm. In total, 40 fiducial markers were implanted, with four markers in each patient, corresponding to one marker in each of the four horizontal quadrants in the esophagus circumference. A mean volume of 82 µL BioXmark® was used per implantation. Table 3 provides further implantation details, including information on perioperative BioXmark® visibility.

Locating BioXmark® and measuring distance to the tumor

The surgeon's proposed resection line was placed 2–6 cm proximally to the line marked by the fiducial marker. After thoroughly scanning the length of the esophagus' exterior *in vivo* with the ultrasound probe, a hyperdense area of approximately 1.5 cm × 1.5 cm was found and concluded to be the fiducial marker. This line was marked with a sterile marker, and the differences between the two purple lines were measured (Figure 1). The hyperdense areas on ultrasound were determined to be the fiducial marker (Figures 2 and 3).

Fiducial markers in the form of hyperdense areas were identified in six of ten patients *in vivo*, corresponding to an *in vivo* success rate of 60%. In two of these six patients, fiducial markers were also found *ex vivo*. In the remaining four patients, the fiducial marker was not found *ex vivo*. In the last four patients, no fiducial markers could be identified *in vivo* or *ex vivo*.

Safety

No adverse events, device deficiencies, or clinically relevant worsening related to BioXmark® were observed in this study. These included the perioperative and postoperative events.

DISCUSSION

This is the first study to investigate the use of a liquid fiducial marker to improve resection margins in patients with esophageal cancer. Ten patients with gastroesophageal tumors were marked endoscopically with a fiducial marker 5 cm proximal to the tumor before surgery.

In this study, successful BioXmark® implantation was achieved in all ten patients, with the identification of the fiducial marker observed on perioperative ultrasound in six of ten cases. The surgeon consistently positioned the proposed resection line proximally to the recommended 5-cm distance from the tumor's proximal boundary. The proposed resection line was placed 2–6 cm proximally *in vivo* to the line marked by the fiducial marker. Following Danish guidelines, the surgeon identified the tumor by digitally palpating the exterior of the esophagus, which is not a precise or reproducible method to achieve R0 resection. Despite the Danish guidelines calling for a 5-cm distance proximally from the tumor to resection, the standard procedure at Rigshospitalet typically involves resection at the level of the azygous vein or higher, if needed. The operating surgeon checks the preoperative scans, and unless these indicate otherwise, the resection is performed at the level of the azygous vein. Notably, in this study, the observed mean macroscopic resection line was 45 mm from the proximal edge of the tumor *ex vivo*, despite all resection lines being placed proximally to the fiducial marker. However, tissue shrinkage after resection is important. One study found that the proximal resection margins of GEJ tumors can shrink to 32% after formalin fixation[13]. The overall length from the *in vivo* specimen to the fixed specimen may decrease by 50%, and despite maximal stretching of the resected unfixed specimen, restoration of only 86% of its original *in vivo* length is possible[13]. This indicates that the aforementioned strategy of resecting at the level of the azygous vein should satisfy the 5-cm distance from the proximal tumor border to resection when considering tissue shrinkage.

Generally, when determining the resection margin in a cancer operation, a surgeon must consider two viable options. If the resection is made too close to the tumor, the risk of R1 resection increases and is associated with increased morbidity and mortality rates. Finding the right distance to the tumor is a challenge, with the recommendations varying worldwide and with the added risk of "skip" metastases[5]. Even with R0 resection, the survival rates decrease if the resection margin is less than 3.8 cm proximal to the tumor[5]. Conversely, if the resection is too extensive, the risk of a poorly perfused conduit increases, and postoperative complications such as anastomotic leakage increase, potentially lowering long-term survival rates[14,15]. Hypothetically, marking of the proposed 5 cm distance from the most proximal part of the tumor could be a useful intraoperative tool when determining the most optimal place to transect the esophagus. This is especially relevant in more extensive resections, where perfusion worsens due to the length of the gastric conduit. One study demonstrated the superiority of indocyanine green fluorescence angiography (ICG-FA) in assessing intraoperative perfusion in GEJ cancer, which can be used to increase the chance of sufficient perfusion[16]. ICG-FA is a promising tool for assessing perfusion but has not yet been used as a standard to identify cancer tissue. However, if one could combine

Table 1 Baseline characteristics of study participants, *n* (%)/mean ± SD

Characteristic	Study population *n* = 10
Age, years	68 ± 6.9
Sex	
Male	8 (80)
Female	2 (20)
ASA	
ASA score: 2	3 (30)
ASA score: 3	7 (70)
cT1[1]	0 (0)
cT2	3 (30)
cT3	5 (50)
cT4	2 (20)
cN0[1]	5 (50)
cN1	3 (30)
cN2	2 (20)
Surgical procedure: Hybrid esophagectomy	8 (80)
Surgical procedure: Open esophagectomy	2 (20)

[1]TNM classification of malignant tumors.
ASA: American society of anesthesiology.

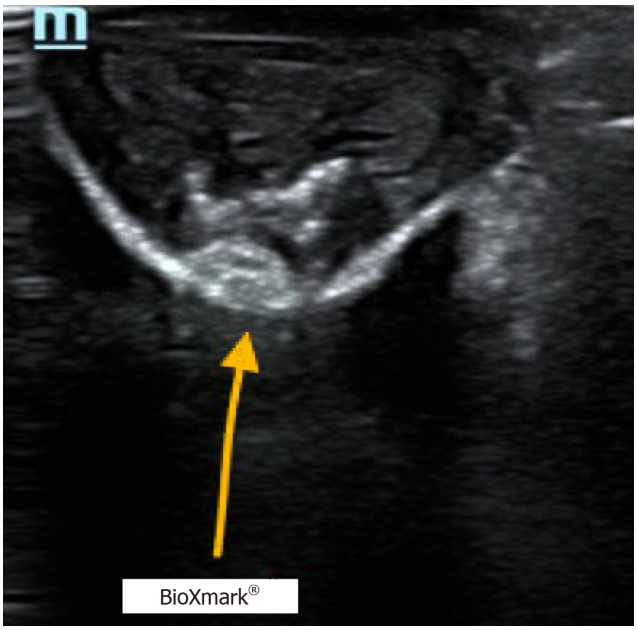


Figure 1 Fiducial marker on intraoperative ultrasound, with the probe placed on the exterior of the esophagus during the right thoracotomy portion of the operation, before resection.

the knowledge of the optimally perfused tissue by ICG-FA and the optimal transection line with a fiducial marker, the number of safer and effective resections could increase.

The decision of where to perform the resection is typically based on national or international guidelines, such as the Danish guidelines[4]. However, these guidelines neglect to consider the effect of neoadjuvant treatment on tumor size and the intraoperative identification of tumor margins. Furthermore, patient-specific conditions, such as esophageal length, concurrent Barrett's disease, and other diseases may affect where one would set the resection margin. In our study, Barrett's dysplasia was present in two out of ten histopathological specimens. Barrett's dysplasia is not palpable;

Table 2 Histopathology and operation details, *n* (%)/mean ± SD

Characteristic	Study population *n* = 10
Tumor type: Adenocarcinoma	8 (80)
Tumor type: Mixed neuroendocrine non-neuroendocrine neoplasm	1 (10)
Tumor type: Mucoepidermoid carcinoma	1 (10)
pT1[1]	4 (40)
pT2	1 (10)
pT3	5 (50)
pN0[1]	5 (50)
pN1	3 (30)
pN2	2 (20)
Tumor regression scoring according to Mandard, 2	3 (30)
Tumor regression scoring according to Mandard, 3	4 (40)
Tumor regression scoring according to Mandard, 4	1 (10)
Tumor regression scoring according to Mandard, 5	1 (10)
No neoadjuvant treatment	1 (10)
Tumor size in millimeters	32.7 ± 23.8
Palpable tumor, yes	7 (70)
Palpable tumor, no	3 (30)
Microscopic distance to proximal tumor resection line, mm	37.3 ± 17.9
Macroscopic distance to proximal tumor resection line, mm	45.3 ± 17.3
R0 resection	10 (100)
R1 resection	0 (0)
Barrett's dysplasia in resected tissue	2 (20)
No Barrett's dysplasia in resected tissue	8 (80)

[1]TNM classification of malignant tumors.

Table 3 Implantation details, *n* (%)/mean ± SD

Characteristic	Study population *n* = 10
Distance from incisors to proximal tumor border, cm	39.3 ± 5.8
Distance from surgeon's proposed proximal resection line to BioXmark®, cm[1]	3.8 (± 1.1)
Number of implantations per patient	4
Amount of BioXmark® per implantation, μL	82 ± 17.5
BioXmark® visible on intraoperative ultrasound *in vivo*	6 (60)
BioXmark® not visible or missing data on intraoperative ultrasound *in vivo*	4 (40)
BioXmark® visible on intraoperative ultrasound *ex vivo*	3 (30)
BioXmark® not visible or missing data on intraoperative ultrasound *ex vivo*	7 (70)

[1]A positive value means the line was proximal to BioXmark®, and a negative value means the line was distal to BioXmark®.

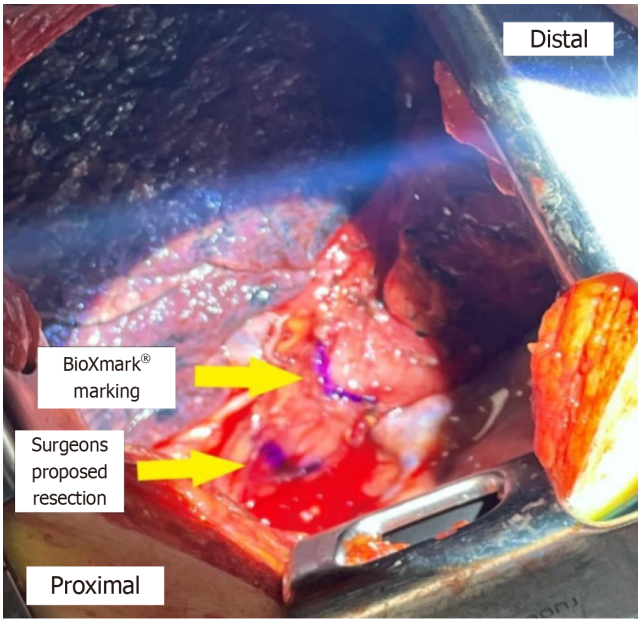


Figure 2 Macroscopic view during the right thoracotomy portion of the operation, with the two resection lines marked with a sterile pen, before resection.

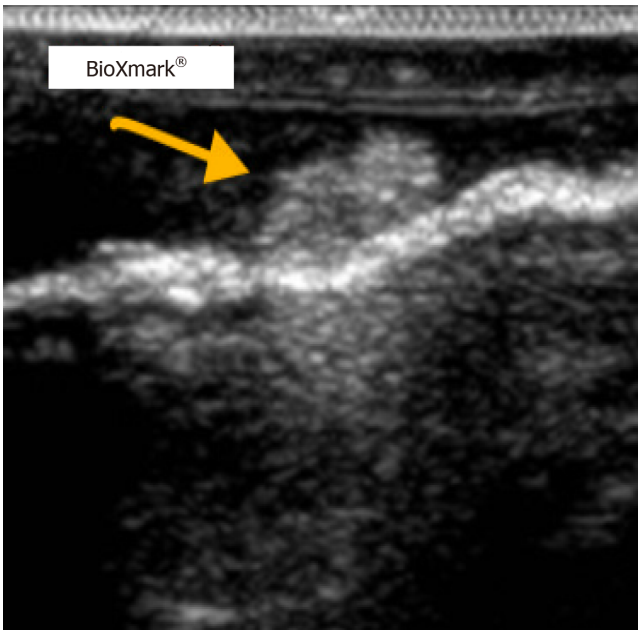


Figure 3 Fiducial marker on intraoperative ultrasound, with the probe placed on the exterior of the esophagus during the right thoracotomy portion of the operation, before resection.

therefore, an increased risk of an insufficient proximal resection margin exists. Individuals diagnosed with Barrett's esophagus, whether with low-grade or high-grade dysplasia, face an elevated annual risk of developing esophageal adenocarcinoma[17,18]. These patients should have their Barrett's esophagus segment resected or undergo regular endoscopic surveillance with biopsies to monitor histopathological changes.

In this study, neither method, resecting at the line of the fiducial marker or resecting at the azygous vein, consistently yielded the recommended 5-cm margin. Although BioXmark® may aid in defining margins beforehand, its ability to secure a specified distance remains uncertain. Attempts to predetermine a 5-cm margin with BioXmark® often resulted in the intraoperative ultrasound identifying a closer proximity to the tumor. Similarly, adhering to the azygous vein resection strategy resulted in a mean resection line of 45 mm, highlighting the difficulty of consistently meeting the desired margin. Addressing this discrepancy between the intended and observed margins is crucial because of its direct impact on R1 resection rates and subsequent patient outcomes. It is imperative to explore refinements or alternative approaches to enhance the precision of these methodologies to minimize R1 resection rates and ultimately improve overall patient survival[5].

The technical feasibility of injecting BioXmark® into organ tissues and its use in radio-guided therapy has been well documented[6-10], and we did not have any difficulties with BioXmark® injection in our study. As we did not have photos or literature available to compare with our findings, we attempted to identify BioXmark® on perioperative ultrasound. In four patients, we could not identify markers *in vivo* or *ex vivo*. This was attributed to migration of the fiducial marker *in vivo*, the small amount injected, or challenges in properly identifying the marker *via* ultrasound. Another reason could be incorrect use of the product, as we injected saline prior to injection of the fiducial marker, and complete solidification could not be ensured because the marker was placed directly before the start of the operation. This could have affected the product's properties and should be carefully considered in future studies. Saline injections were administered to prevent transesophageal placement of the marker by lifting the submucosa. Although several studies have been published on the use of BioXmark®, none have investigated the use of BioXmark® during surgery or its visibility on ultrasound within a brief period after placement.

One study investigated the use of BioXmark® in a prospective feasibility study of 20 patients with rectal cancer[6]. Their findings demonstrated the positional stability of BioXmark® on computed tomography (CT) for use in image-guided radiotherapy, albeit with poor visibility on MRI. Similar results were observed in another study of image-guided radiotherapy for bladder cancer[7]. This study found that BioXmark® is easy to inject, visible on CT, positionally stable, and safe. One study on ten patients with esophageal cancer found that the implantation of BioXmark® was technically feasible, with appropriate visibility on CT, cone beam CT, and MRI, with excellent positional stability[8].

A limitation of this study is the short interval between implantation and ultrasound. Hypothetically, the difficulty in locating BioXmark® in this study could be due to insufficient time for the marker to harden or the use of a saline deposit. BioXmark® is a viscous substance that hardens *in vivo* as ethanol diffuses out of the marker; however, no information is available on the kinetics or duration of this process. Thus, the risk of marker migration or flattening into a thin sheet *in vivo* is likely high. This was a quality assurance study aimed at evaluating the first cases of a newly introduced procedure, and the specialists performing the ultrasound identification of the fiducial marker were surgeons, not radiologists. Furthermore, the surgeons had no prior experience of visualizing and identifying the fiducial marker. Moreover, the problem of insufficient time for markers to harden was first discovered after placing the fiducial marker. Endoscopic ultrasound could have been used to provide real-time imaging of the injection location; however, due to logistical difficulties, this was not possible. The fiducial marker BioXmark® is not intended for immediate ultrasound identification after injection, which could further explain the difficulties in locating the marker. A prospective study is currently underway, wherein BioXmark® is administered prior to chemotherapy. This approach enables the surgeon to macroscopically visualize the tumor during marker injection, thereby significantly enhancing the precision of marker placement. Additionally, the extended interval between injection and perioperative ultrasound identification should facilitate marker hardening, potentially improving visibility on perioperative ultrasound.

CONCLUSION

In conclusion, we found limited visibility of BioXmark® on intraoperative ultrasound after preoperative injection and neoadjuvant treatment. Despite the ease of its technical implantation, locating the fiducial marker was successful in only six patients. Further studies are needed to explore the potential clinical applications of fiducial liquid markers in cancer surgery. Fiducial markers have myriad applications in clinical settings, with potential uses across both medical and surgical specialties. Initial costs with implementation should be compared with the possible benefits such as reduced reoperation rates, improved patient outcomes, and ultimately reduced use of healthcare resources.

FOOTNOTES

Author contributions: Solstad TU, Achiam MP, and Olsen AA initiated and designed the study; Solstad TU, Mucha AW, Grossjohann H, and Achiam MP acquired the data and performed the research; Solstad TU, Mucha AW, Olsen AO, and Achiam MP analyzed and interpreted the data; Solstad TU, Mucha AW, and Olsen AO drafted the manuscript; Solstad TU, Mucha AW, Grossjohann H, Olsen AO, and Achiam MP revised and contributed to the final manuscript. All authors have read and approved the final manuscript.

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Institutional review board statement: As BioXmark® was implemented as a standard supplement to the standard operating procedure for esophagectomies at Rigshospitalet, the study did not constitute a clinical trial or experimental research requiring prior ethics committee approval. Instead, it was classified as a quality assurance initiative.

Informed consent statement: As BioXmark® was implemented as a standard supplement to the standard operating procedure for esophagectomies at Rigshospitalet, the study did not constitute a clinical trial or experimental research requiring prior ethics committee approval. Instead, it was classified as a quality assurance initiative.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The data that support the findings of this study are available on reasonable request from the corresponding

author. The data are not publicly available due to privacy or ethical restrictions.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Retrospective Study

Transcatheter atrial septal defects and patent foramen ovale closure: Medicare utilization and reimbursements

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Abstract

BACKGROUND

The Food and Drug Administration has approved percutaneous atrial septal defect (ASD) and patent foramen ovale (PFO) closure devices for hemodynamically significant interatrial shunts, paradoxical emboli including stroke, and decompression sickness. We aimed to study the trends in utilization and reimbursements of transcatheter ASD/PFO closure devices.

AIM

To analyze trends in utilization and Medicare reimbursements for transcatheter ASD/PFO closure procedures from 2013 to 2022.

METHODS

A query of administrative data on United States Medicare beneficiaries undergoing transcatheter ASD/PFO was conducted from 2013 to 2022 using the Centers for Medicare and Medicaid Services Part B National Summary Data File. Inflation adjustments were made using the 2023 Consumer Price Index. Trend analysis was quantified using growth rate and simple linear regression calculations. All analyses were performed using Microsoft Excel 16.77.1 (2023).

RESULTS

The annual number of transcatheter ASD/PFO closure procedures increased by 81% since 2013, with an average yearly growth rate of 44% cases per year ($P <$

0.001). Annual Medicare reimbursements for transcatheter ASD/PFO therapies mirrored the annual procedure trends. The per-case reimbursements decreased by 18%, *i.e.*, $1128.80 in 2013 and $ 770.21 in 2022 ($P < 0.001$). There was a significant drop in the number of procedures in the year 2020, which correlates to the onset of the coronavirus disease 2019 pandemic, followed by a sharp uptick in the number of cases in 2021 and 2022.

CONCLUSION

Medicare utilization of transcatheter ASD/PFO closure therapies has grown significantly in procedural volume from 2013 to 2022. However, this has been accompanied by a decrease in per-case reimbursements.

Key Words: Atrial septal defect; Patent foramen ovale; Medicare; Reimbursement; Patent foramen ovale closure

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Core Tip: From 2013 to 2022, the volume of transcatheter atrial septal defect (ASD)/patent foramen ovale (PFO) closure procedures in Medicare beneficiaries rose by 81%, with an average annual growth rate of 44%. While annual Medicare reimbursements paralleled this trend, per-case reimbursements decreased by 18%, from $1128.80 in 2013 to $770.21 in 2022. A significant decline in procedures was observed in 2020, coinciding with the coronavirus disease 2019 pandemic, followed by a sharp increase in 2021 and 2022. These results underscore a growing demand for ASD/PFO therapies, despite a reduction in reimbursement rates.

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INTRODUCTION

Defects in the septum primum or secundum cause atrial septal defect (ASD), and defects in postnatal closure between these septums lead to patent foramen ovale (PFO)[1]. Iatrogenic ASD (iASD) is a complication of interventional procedures utilizing transeptal puncture (TSP) and dilatation of the inter-atrial septum with an incidence of 0%–50%[2].

The only strong recommendation for ASD/PFO closure is for cryptogenic stroke in patients aged 18-60 years with a high pretest probability[3]. Off-label indications include cryptogenic stroke in patients over 60 years, migraine with aura, decompression sickness, platypnea orthodeoxia syndrome, and PFO in liver transplant patients, where shared decision-making is crucial[4,5].

The Food and Drug Administration (FDA) approved the use of percutaneous ASD devices for PFO closure in 2017, four years after the promising results noted in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial[6].

This paper aimed to study the trends in utilization and reimbursements of transcatheter ASD/PFO closure devices.

MATERIALS AND METHODS

This cross-sectional study assessed the utilization and reimbursement trends of transcatheter ASD/PFO closure in the US Medicare population from 2013 to 2022 using publicly available administrative data. Analysis began with the year 2013 because it was the first full year after the results of the RESPECT trial compared the Amplatzer PFO occluder to medical therapy were published[7]. All data were accessed online at http://www.cms.gov under Research, Statistics, Data and Systems. National-level procedural data were assessed using Centre of Medicare Services (CMS) Part B National Summary Data File, which represents about 62% of all Medicare beneficiaries, about 15% younger than 65 years and 78% with incomes above 135% of the federal poverty level[8]. The sample accurately represents male and female proportions but underrepresents the Black and Latino population compared with the national demographics[9]. The CMS Medicare Enrollment Reports were used to identify the annual number of national-level Medicare enrollees. Inflation adjustments were made using the 2023 Consumer Price Index[10]. Using the billed American Medical Association Current Procedural Terminology codes, Percutaneous transcatheter closure of congenital interatrial communication (93580) data was extracted from the Part B National Summary Data File. The annual number of procedures and annual Medicare reimbursement were summated. To assess the year-to-year variability an annual percentage change analysis was performed. Annual per-case reimbursement was calculated by dividing the annual reimbursement by the annual number of procedures. Trend analysis was quantified using growth rate and simple linear regression calculations[11].

Statistical analysis

All analyses were performed using Microsoft Excel 16.77.1 (2023). These data did not have any patient identifiers and are available to the public and, therefore, did not require review from any institutional review board.

RESULTS

Procedures

From 2013 to 2022, the total volume of transcatheter ASD/PFO closure procedures increased by 81%. However, annual trends saw fluctuations, with notable year-on-year declines in 2014 and 2015 before a consistent upward trajectory in subsequent years, with an average yearly growth rate of 44% cases per year ($P < 0.001$)[12]. The observed decline in transcatheter PFO closure procedures during 2014 and 2015 is likely due to emerging clinical trial data that questioned the efficacy of PFO closure for stroke prevention[13]. From 2014 to 2016 (2013 was used as a reference year), the average growth rate remained between -7.74% to 8.77%, but from 2017 to 2022, the annual average growth rate changed significantly from 25.15% to 81.05%, with a sharp percentage drop-in growth rate noticed in the year 2020 to 59.88% from an annual growth rate of 91% in 2019. However, the magnitude of growth rate changes continued to remain quite significant as compared to the year 2013 (Table 1 and Figure 1).

Table 1 The annual number of services, charges, and payments, along with the inflation-adjusted average rate of reimbursement per procedure and the average annual growth rate of the procedure, is depicted below

Year	Procedure/services	Charges	Payment	Inflation adjusted average rate	Annual growth rate of reimbursement[1]	Annual growth rate of procedures[2]
2022	2455	$2319536.28	$1818140.15	$770.21	-46.56	81.05
2021	2449	$2333765.36	$1860376.25	$835.61	-25.97	80.61
2020	2168	$2130582.64	$1693305.75	$890.39	-21.12	59.88
2019	2590	$2564044.60	$2010862.74	$908.38	-19.53	91.00
2018	2260	$2225464.21	$1725140.80	$923.64	-18.17	66.67
2017	1697	$1672085.09	$1293973.58	$953.13	-15.56	25.15
2016	1475	$1435750.68	$1112748.71	$995.82	-11.78	8.77
2015	1311	$1286539.46	$1000438.04	$1045.46	-7.38	-3.32
2014	1251	$1233624.63	$952857.12	$1142.51	1.21	-7.74
2013	1356	$1312737.26	$1020439.87	$1128.81		

[1]Depicts annual percentage change in reimbursements per case for transcatheter atrial septal defect/patent foramen ovale closure procedures.
[2]Depicts annual percentage change in transcatheter atrial septal defect/patent foramen ovale closure procedures. *P* value < 0.01 after linear regression analysis.

Reimbursements

Annual Medicare reimbursements for transcatheter ASD/PFO therapies mirrored the annual procedure trends. The per-case reimbursements decreased by 18%, *i.e.*, $1128.80 in 2013 and $770.21 in 2022 ($P < 0.001$)[12,14,15]. Assessing per case year-to-year variability, annual percentage change for reimbursement decreased consistently from -7.38% in 2015 to -46.56% in 2022, with the most significant percentage per case decrease in 2022 as depicted in Table 1 and Figure 2.

DISCUSSION

Our study provides a ten-year national-level analysis of the utilization and reimbursement of transcatheter ASD/PFO closure devices. These therapies' utilization and annual procedure volume increased by 81% in 2022 compared to 2013, while the average annual per-case reimbursements decreased by 18% from 2013 to 2022[16]. The observed decline in transcatheter PFO closure procedures during 2014 and 2015 was likely due to emerging clinical trial data that questioned the efficacy of PFO closure for stroke prevention[17]. Furthermore, clinical trials such as the CLOSURE I trial published in 2012, did not demonstrate a significant benefit of PFO closure over medical therapy[18]. Thereafter, procedure volume trend increase was generally consistent over the years apart from the drop noticed in the year 2020, likely due to the coronavirus disease 2019 (COVID-19) pandemic[19].

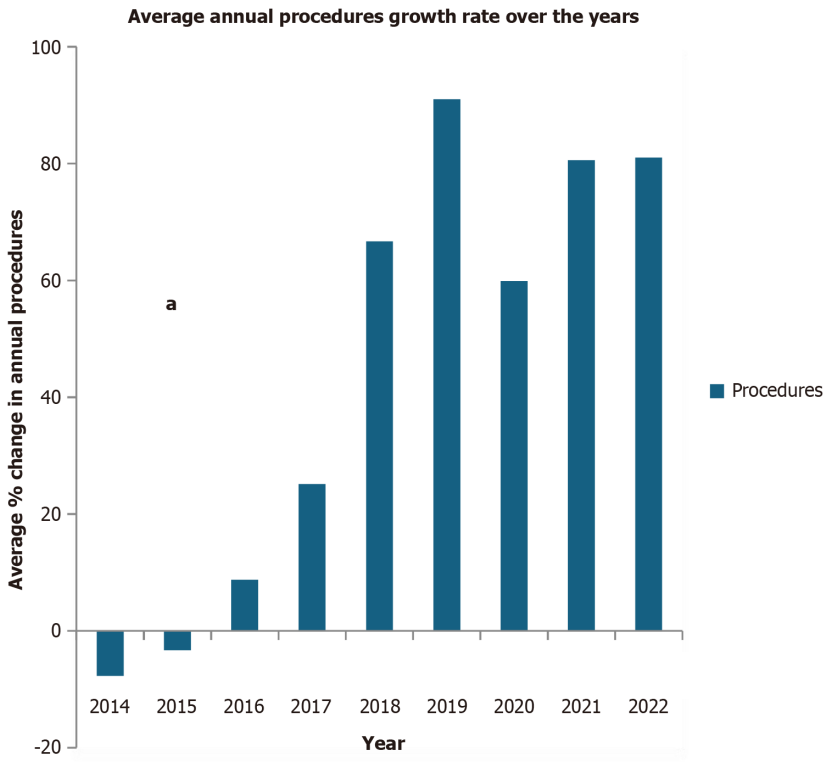


Figure 1 Average annual percentage procedures of transcatheter atrial septal defect/patent foramen ovale closure device. [a]*P* < 0.001.

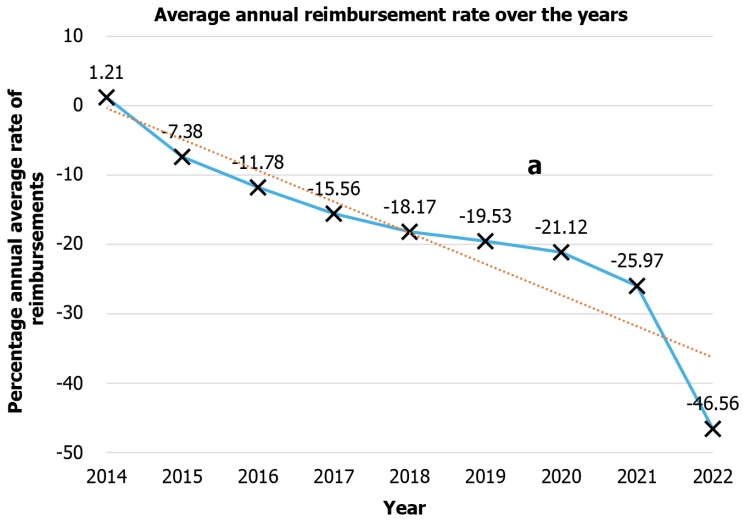


Figure 2 Average annual percentage reimbursements per case for transcatheter atrial septal defect/patent foramen ovale closure procedures. [a]*P* < 0.001.

Randomized controlled trials like Patent Foramen Ovale Closure or Anticoagulants *vs* Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE), Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy After Stroke (RESPECT) and Patent Foramen Ovale Closure or Antiplatelet for Cryptogenic Stroke (REDUCE), published in 2017, supporting PFO closure, resulting in the approval of these devices. Our study utilized the CMS Part B National Summary Data File, which meant that 85% of the population in our study was over 65 years old. Interestingly, there was a 91% increase in annual device closure procedure volume between 2013 and 2019, with a sharp rise being noted from 2017 since the results of the CLOSE trial and FDA approval, which is similar to a previous study from the National Inpatient Sample showing a significant increase in transcatheter ASD/PFO closure from 2016 to 2019[20]. This increase coincided with the rise in Transcatheter Mitral Valve Edge-to-Edge Repair (TEER) procedures, which saw an almost tenfold increase from 2014 to 2019[21]. This surge likely led to a higher detection rate of iatrogenic ASD and subsequent closures[22]. We also noted a drop in the surge and number of procedures performed in 2020, likely due to the COVID-19 pandemic[23]. However, with more data, we believe that the findings of increased ASD/PFO closure indicate a second look into the indications of the physicians performing these procedures, if they are not related to the increase in TEER procedure

volume[24,25].

Trends in total Medicare reimbursement reflected trends in the number of procedures. Conversely, per-case reimbursement dropped by 46.5% from 2013 to 2022, with a brief increase in 2014. Similar reimbursement trends were observed in neurosurgery, hematology/oncology, and interventional radiology[26-28]. This reduction in per-case reimbursement could be attributed to the Medicare conversion factor (MCF) not consistently matching inflation over the last decade[11]. The MCF is also influenced by budget neutrality requirements, legislative adjustments, and the implementation of policies like the Medicare Access and CHIP Reauthorization Act, which was introduced in 2015 to stabilize the conversion factor with modest annual increases that have not always kept pace with medical inflation[29,30]. Additional reasons for the decline in reimbursements include reduction in hospital stay, decline in the cost of medical procedures and consumables, increased efficiency and maturity of medical technology and procedures, and changes in reimbursement models[31-33].

CONCLUSION

Medicare utilization of transcatheter ASD/PFO closure therapies has grown significantly in procedural volume from 2013 to 2022. However, this has been accompanied by a decrease in per-case reimbursements. Increasing the number of services while reducing overall physician compensation could potentially create access challenges for Medicare beneficiaries. Further studies delineating the indications for PFO closure and randomized controlled trials addressing the usefulness of PFO closure in populations over 60 years of age can strengthen recommendations and ultimately improve appropriate use.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Machine learning for patient selection in corticosteroid decision making in knee osteoarthritis: A feasibility model

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Abstract

BACKGROUND

Relieving pain is central to the early management of knee osteoarthritis, with a plethora of pharmacological agents licensed for this purpose. Intra-articular corticosteroid injections are a widely used option, albeit with variable efficacy.

AIM

To develop a machine learning (ML) model that predicts which patients will benefit from corticosteroid injections.

METHODS

Data from two prospective cohort studies [Osteoarthritis (OA) Initiative and Multicentre OA Study] was combined. The primary outcome was patient-reported pain score following corticosteroid injection, assessed using the Western Ontario and McMaster Universities OA pain scale, with significant change defined using minimally clinically important difference and meaningful within person change. A ML algorithm was developed, utilizing linear discriminant analysis, to predict symptomatic improvement, and examine the association between pain scores and patient factors by calculating the sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and F2 score.

RESULTS

A total of 330 patients were included, with a mean age of 63.4 (SD: 8.3). The mean Western Ontario and McMaster Universities OA pain score was 5.2 (SD: 4.1), with

only 25.5% of patients achieving significant improvement in pain following corticosteroid injection. The ML model generated an accuracy of 67.8% (95% confidence interval: 64.6%-70.9%), F1 score of 30.8%, and an area under the curve score of 0.60.

CONCLUSION
The model demonstrated feasibility to assist clinicians with decision-making in patient selection for corticosteroid injections. Further studies are required to improve the model prior to testing in clinical settings.

Key Words: Knee osteoarthritis; Machine learning; Predictive modelling; Corticosteroid injection; Patient selection

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Core Tip: Historically, the efficacy of corticosteroid injections in knee osteoarthritis has been heavily debated, as patient responses can vary significantly. This study evaluates the feasibility of a machine learning model to identify which patients with knee osteoarthritis will benefit from corticosteroid injections. Data from two cohort studies were combined for analysis. The model generated an accuracy of 67.8% (95% confidence interval: 64.6%-70.9%), F1 score of 30.8%, and an area under the curve score of 0.60. These metrics demonstrate feasibility to assist clinicians with decision-making in patient selection for corticosteroid injections. Further research is required to improve the model prior to testing in clinical settings.

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INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disorder characteristic by progressive loss of articular cartilage, and a leading cause of pain and disability worldwide[1]. Knee OA represents the overwhelming majority of the disease burden[2]. Its presentation can vary, but the cardinal features are joint pain, impaired day-to-day functioning, and a diminished quality of life[3]. Factors influencing variations in symptoms among patients include age, gender, body habitus, genetic predisposition, muscle weakness, prior injuries or comorbidities, and job requirements[4]. Prior to end-stage disease, which usually requires knee replacement surgery, management involves a multidisciplinary approach using both non-pharmacological and pharmacological interventions to optimize symptom control and limit disease progression[3]. Non-pharmacological interventions such as patient education, weight loss, and muscle strengthening exercises form the foundational layer of management[3,5]. Whilst pharmacological agents are central to pain management, non-steroidal anti-inflammatory drugs, paracetamol, opioids, and antidepressants amongst the most frequently used agents[5,6].

Intra-articular corticosteroid injections are an alternative pharmacological method of managing the debilitating pain in knee OA, serving as the middle ground between oral analgesics and surgical intervention[5]. Commonly used in patients with knee OA, with seven million performed annually in the US alone, there remains much debate regarding its efficacy, particularly the extent of its benefits[7]. Raynauld *et al*[8] demonstrated improvements in night pain ($P < 0.05$) and stiffness ($P < 0.05$) at two-year follow-up in 34 patients receiving 40 mg triamcinolone acetate injections every three months compared to patients receiving placebo, supporting its role in long-term pain control. However, in a study by Jones *et al*[9], 59 patients with knee OA received a single 40 mg injection of methylprednisolone acetate. Whilst the treatment produced a significant improvement in visual analog scale pain scores at three weeks compared to baseline, with a median change of -2 points (interquartile range: -16.25 to 4.0, $P < 0.05$), these benefits were not sustained at eight-week follow-up. There was no change in median visual analog scale score compared to baseline (interquartile range: -14.5 to 8.0, $P > 0.05$), suggesting its benefits are short-lived[9]. Corticosteroids also have potential side-effects, including local infection, joint destruction, muscle atrophy, and tendon rupture[5,10].

Machine learning (ML) employs algorithms to analyze large datasets and identify patterns[11]. These algorithms can be used to assist clinical decision making, enabling a more personalized approach to patient care which translates into improved patient outcomes[12]. In the context of knee OA, its application has been described at various stages: To guide clinical decision-making, including predicting early diagnosis, disease progression, and the need for total knee replacement[13-15]. However, no studies have explored the use of corticosteroid injections in knee OA using ML models. This study, therefore, aims to develop a ML algorithm to identify which patients with knee OA will benefit from corticosteroid injections.

MATERIALS AND METHODS

Design

This study is a secondary analysis of the Multicentre OA Study (MOST) and the OA Initiative (OAI) datasets. MOST is a longitudinal, prospective observational study funded by the National Institute on Aging in the United States[16]. The aim of the MOST study was to evaluate factors that can affect prognosis in patients with knee OA. Patients between the ages of 50 to 79 were selected based on having pre-existing knee OA or being at high risk of knee OA[16]. The OAI is also a longitudinal, prospective observational study funded by the National Institute of Health and the private sector. Recruitment criteria included male or female patients between the ages of 45 to 79 with symptomatic knee OA or an increased risk of developing it during the study.

MOST data collection

Data collection began in 2003 and included 3026 patients at baseline[16]. Data collected include demographic data, medical history, joint symptoms, functional status, disability, mental health, physical performance, radiological findings, and medication/supplement history. Participants that were recruited were seen at one of the two centres for baseline clinical examinations, administration of self-reported health questionnaires, knee imaging (magnetic resonance imaging and X-ray), whole-body dual X-ray absorptiometry (DXA), and blood and urine specimens. Follow-up assessments occurred at 15 months, 30 months, 60 months, 72 months, and 84 months after recruitment with a mixture of telephone interviews and clinic visits[16].

OAI data collection

Data collection began in 2004 and included 4796 patients at baseline[17]. The OAI dataset consists of demographic data, joint symptoms, pain scores, functional status, mental health, physical performance, radiological findings, past treatments, and biological specimens. The OAI cohort underwent a comprehensive assessment schedule over an eight-year period, including in-clinic visits with biospecimen collection and imaging at baseline, 12 months, 24 months, 36 months, and 48 months. Mailed questionnaires and telephone interviews were conducted at 60 months and 84 months, while the 72-month visit included in-clinic biospecimen collection and imaging[17].

Inclusion and exclusion criteria

In this study, only patients who received intra-articular corticosteroid injections were included in the analysis. Data were collected on variables that can affect prognosis in knee OA. This included age, sex, ethnicity, body mass index (BMI)[18], comorbidities[19], X-ray findings (Kellgren Lawrence grade)[19,20], pain catastrophizing score[21,22], physical activity level score[23], presence of symptoms in the affected knee[19], baseline Western Ontario and McMaster Universities OA (WOMAC) index pain score[24], and whether patients had received corticosteroid injections in the past. Patients had multiple entries if they received treatment on more than one knee or received treatment multiple times throughout the data collection period as this represented a different event time point.

Primary outcome

The primary outcome in this study was patient-reported pain levels using the WOMAC index scale[24]. This scale evaluates pain severity during five activities of daily living: Walking, climbing stairs, sleep disturbance, sitting, lying, and standing. Knee pain in each of these situations is ranked on a 5-point scale ranging from "none" (0 points) to "extreme" (4 points), with a maximum overall score of 20 points[25,26]. Clinically significant change in pain scores was defined as any change considered clinically relevant across a population (minimally clinically important difference (MCID) or an individual person (meaningful within person change (MWPC))[27,28]. In this study, as established in the literature, a difference of five points in the WOMAC pain scale was used as the MCID, and a change of 12.5% for MWPC[28,29]. Treatment was considered successful if the patient achieved MCID or MWPC.

ML algorithm

A supervised classification algorithm was developed, utilizing linear discriminant analysis (LDA). LDA is a subspace method that involves projecting the original hyperdimensional data onto a lower-dimensional space in order to maximize the class separation, whilst also preserving key discriminative information between each class, allowing for optimal analysis of a dataset with a large number of variables[30]. In this analysis, age, presence symptoms, baseline WOMAC score, Kellgren-Lawrence grade, and physical activity scale for the elderly score were used as inputs in the ML algorithm. These variables were selected as they are established risk factors for the development and progression of knee OA[4]. It was implemented using an 80:20 test: Validation split. Model capabilities were determined using accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F2 score. The experiment was repeated 100 times with the data "shuffled" each time, to ensure the reliability of results. The mean and confidence interval (CI) was then calculated for each metric. Furthermore, the receiver operating characteristic (ROC) curve was plotted to enhance robustness of results, both through visual inspection of the curve and the calculated area under the curve (AUC).

Ethics

For the MOST study, ethical approval was obtained from the Institutional Review Board at each of the core four sites (The University of Iowa, The University of Alabama at Birmingham, The University of California and Boston University)[16,31]. All participants provided informed consent. For the OAI study, ethical approval and informed consent was obtained

from all the participants[17].

RESULTS

Cohort characteristics

The OAI and MOST enrolled 4796 patients and 3026 patients respectively, total 7822 patients. Data were collected at five different timepoints in the MOST study; however, only three of these time points included data on steroid injections, covering 9078 patients. Of these, 290 received a steroid injection, with 71 undergoing bilateral injections, giving a total of 361 entries. Forty-seven knees were removed due to missing radiographic data, leaving a total of 314 entries from the MOST study which met the inclusion criteria. In the OAI study, only one timepoint, with 4796 entries, included outcomes related to corticosteroid injection use. One hundred and five of these patients received a steroid injection, of which 18 were bilateral, making the total number of entries 123. Only 16 entries included all the data required for analysis. In total there were 330 entries from both datasets available for analysis.

The final cohort consisted of middle-aged patients (mean: 63.4 ± 8.3), who were predominantly male (70.6%), Caucasian (79.7%), and overweight (mean BMI: 32.3 ± 6.2). The majority of patients were classified as obese (55.5%), defined as a BMI greater than 30. The mean WOMAC pain score was 5.2 (SD: 4.1). The remaining baseline patient characteristics can be seen in Table 1. As seen in Table 2, there was no significant difference in the age, BMI, sex, and race of patients who achieved a clinically significant change in their WOMAC score compared to those who did not. Comorbidities were more common in patients who did not experience significant improvements in their WOMAC pain score compared to those that experienced significant improvements, but there was no statistical significance to this pattern. Following a similar pattern, there was no significant correlation between the Kellgren Lawrence grade, pain catastrophizing score, or physical activity scale for the elderly score between patients experiencing a significant or non-significant change in their WOMAC pain score.

Performance metrics of LDA model

The overall accuracy of the model was 67.8% (95%CI: 64.6%-70.9%) in identifying patients likely to benefit from intra-articular corticosteroid injections for knee OA. The LDA model had a specificity of 80.8% (95%CI: 77.2%-84.5%) and a sensitivity of 29.6% (95%CI: 23.6%-35.6%). The positive predictive value was 36.2% (95%CI: 28.5%-43.9%) and the negative predictive value 77.6% (95%CI: 74.7%-80.6%). The F1 score was 30.8% and the F2 score was 29.7% (Table 3).

ROC analysis

Figure 1 illustrates the ROC curve and the corresponding AUC. This quantifies the model's ability to distinguish between patients who will likely benefit from corticosteroid injections and those who are not. The dashed red line represents an AUC score of 0.50, indicative of random guessing. The mean AUC of this study is 0.60 which is slightly higher and suggests moderate discriminatory ability.

DISCUSSION

In this study, only 26% of patients were observed to have a meaningful clinically important improvement in pain score following an intra-articular corticosteroid injection for knee OA. An LDA model was developed to identify these patients, with an accuracy of 67.8% (95%CI: 64.6%-60.9%), and an AUC of 0.6, suggesting a moderate ability to predict the outcome. This was reflected in the model's low sensitivity of 29.6% (95%CI: 23.6%-35.6%). In contrast, the high specificity of 80.8% (95%CI: 77.2%-84.5%) suggests it was better at identifying patients who are unlikely to realize any benefits from the injection. Furthermore, the F1 score of 30.8% suggests a considerable imbalance between the model's precision and recall ability.

While no other published studies have reported on the prediction of symptomatic improvement following intra-articular corticosteroid injections for knee OA, the application of ML has been discussed in a wide range of medical settings, some similar in their goals to our study[13,32-34]. For example, in 2019, Huber *et al*[35] compared multiple ML models in their ability to predict patient-reported outcomes in 30524 and 34110 patients undergoing hip and knee replacement surgery respectively. Huber *et al*[35] found the most successful model delivered an AUC score of 0.87, indicating a clinically acceptable ability to discriminate between positive and negative outcomes following knee replacement surgery. Another example is the retrospective study by Wang *et al*[36], who attempted to predict outcomes in 288 patients with cervical foraminal stenosis receiving epidural steroid injections for their radicular pain, using a deep learning algorithm that solely analyzed magnetic resonance imaging data. Their model demonstrated good efficacy, reporting an AUC score of 0.82. Both these studies reported higher AUC scores, which would be considered acceptable for clinical use, compared to our algorithm. A possible reason for our model's lower performance relative to these models is the low number of entries in the dataset (330) and even fewer patients achieving clinically significant change in their WOMAC pain score (84), resulting in a small number of opportunities for the model to detect the already-challenging patterns[37]. The limited sample size likely led to overfitting, where the ML model memorizes patterns within the dataset too closely, and therefore fails to perform adequately on unseen data. This was exacerbated by the extensive variables included in the dataset which may have introduced irrelevant data, often termed as "noise", hindering the LDA model from recognizing meaningful patterns, culminating in its restricted ability to discriminate between the study's outcomes

Table 1 Baseline characteristics of patients included in final analysis

Characteristics	Frequency	Percentage
Age (year), mean ± SD	63.4 ± 8.3	-
Gender		
Male	233	70.6%
Female	97	29.4%
Race		
White/caucasian	263	79.7%
Black/afro-caribbean	59	17.9%
Other	8	2.4%
BMI (kg/m^2), mean ± SD	32.3 ± 6.2	-
BMI < 30	147	44.5%
BMI ≥ 30	183	55.5%
Number of comorbidities, mean ± SD	0.7 ± 1.2	-
Comorbidities ≤ 3	317	96.1%
Comorbidities > 3	13	3.9%
KLG		
KLG < 2	69	20.9%
KLG ≥ 2	261	79.1%
PASE, mean ± SD	163.1 ± 91.6	-
CESD, mean ± SD	9.7 ± 9.1	-
Past steroid use		
No	118	35.8%
Yes	38	11.5%
Unknown	174	52.7%
WOMAC pain score, mean ± SD	5.2 ± 4.1	-
Non-significant change	246	74.5%
Significant change	84	25.5%

BMI: Body mass index; PASE: Physical activity scale for the elderly; CESD: Center for epidemiological studies depression; KLG: Kellgren Lawrence grade; WOMAC: Western Ontario and McMaster Universities Osteoarthritis.

[37,38]. Permutation importance techniques are being increasingly utilized to determine the relevance of variables to the model's predictive goal, enabling the selection of the most pertinent variables and subsequently improving the accuracy of their models[39]. Implementing these techniques in our model design could have helped exclude irrelevant variables from our dataset, thereby reducing noise and its impact on accuracy that follows. Ultimately, our model's performance fell short of the clinically-acceptable AUC threshold of 0.80[40]. At present, it is not suitable for clinical use as a decision-making tool for selecting patients suitable for injections. Its moderate discriminatory ability may lead to a considerable amount of false-positive and false-negative outcomes. Further development of the model is required to enhance its discriminatory and predictive capabilities, aiming for a minimum AUC score of 0.9 to ensure exceptional accuracy.

Accepting these limitations, to the best of our knowledge, this study is the first to use ML to determine which knee OA patients will benefit from non-surgical management study, and has demonstrated the feasibility of this approach to assist in decision-making for patient selection regarding corticosteroid injection therapy for knee OA. This has the potential for clinical and economic significance, given that more than seven million corticosteroid injections are performed annually in the United States alone, with a traditional trial-and-error approach, rather than the personalized approach that would be facilitated by an improved version of our algorithm[12,41]. With our robust and reproductible methodology, this study provides a platform for future research to build on our findings, with the aim of developing a model that can accurately assist clinicians in decision making regarding the use of corticosteroid injections. It will also be crucial in incentivizing model development to examine various other management options for knee OA, such as hyaluronic acid and chondroitin sulphate supplements, both of which exhibit contentious efficacy[42].

Table 2 Data showing the characteristics of patients that achieved significant and non-significant change in Western Ontario and McMaster Universities Osteoarthritis pain scores, *n* (%)

Characteristics	Meaningful clinical significant change (MCID or MWPC)		Pearson correlation coefficient	*P* value
	No	Yes		
Age (year), mean ± SD	63.1 ± 7.8	64.3 ± 9.5	0.062	0.259
Gender			0.005	0.932
Male	174 (70.7)	59 (70.2)		
Female	72 (29.3)	25 (29.8)		
Race			-0.016	0.772
White/caucasian	199 (80.9)	64 (76.2)		
Black/afro-caribbean	40 (16.3)	19 (22.6)		
Other	7 (2.8)	1 (1.2)		
BMI (kg/m^2), mean ± SD	32.2 ± 6.2	32.4 ± 6.4	0.0150	0.786
BMI < 30	114 (46.3)	36 (42.9)		
BMI ≥ 30	132 (53.7)	48 (57.1)		
Number of comorbidities, mean ± SD	0.7 ± 1.1	0.7 ± 1.3	0.006	0.919
Comorbidities ≤ 3	239 (97.2)	78 (92.9)		
Comorbidities > 3	7 (2.8)	6 (7.1)		
KLG			0.034	0.537
KLG < 2	53 (21.5)	15 (17.9)		
KLG ≥ 2	193 (78.5)	69 (82.1)		
PASE, mean ± SD	159.8 ± 84.7	172.8 ± 109.5	0.062	0.262
CESD, mean ± SD	9.5 ± 8.6	10.2 ± 10.2	0.034	0.543
Past steroid use			-0.013	0.820
No	90 (36.6)	28 (33.3)		
Yes	25 (10.2)	13 (15.5)		
Unknown	131 (53.2)	43 (51.2)		
WOMAC pain score, mean ± SD	5.0 ± 4.9	5.8 ± 4.1	0.084	0.128

MCID: Minimally clinically important difference; MWPC: Meaningful within person change; BMI: Body mass index; KLG: Kellgren Lawrence grade; PASE: Physical activity scale for the elderly; CESD: Center for epidemiological studies depression; WOMAC: Western Ontario and McMaster Universities Osteoarthritis.

Limitations

As discussed, the main limitation of our study is the small number of patients eligible for inclusion, and the even smaller number of those benefitting from a corticosteroid injection. The dataset may not have included the core variables that impact response to corticosteroids, further restricting the model's overall performance. Moreover, neither MOST or OAI provided adequate information regarding when corticosteroid injections were administered during their respective study timelines. Given the minimum 12-month intervals between patient assessments, coupled with the short-term analgesic benefits of corticosteroid injections[9], some patients may have experienced a significant improvement in WOMAC score initially, but these effects may have not been sustained at follow-up. This introduces bias, limiting the validity of the datasets, and in turn hindering the predictive accuracy of our model. Incorporating a standardized approach, such as limiting injections to a maximum three doses per annum at minimum three-month intervals, as per current guidelines [43], combined with more frequent follow-up, would maximize analgesic effect, improve assessment of its effectiveness, and ultimately maximize model performance. Furthermore, incorporating objective assessments, such as monitoring patients' ability to stand and walk at pre-specified intervals would provide a more comprehensive assessment of immediate and sustained therapeutic effectiveness.

Table 3 Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and F-scores of the linear discriminant analysis model

Parameter	Mean	95%CI
Sensitivity	29.6%	23.6%-35.6%
Specificity	80.8%	77.2%-84.5%
Positive predictive value	36.2%	28.5%-43.9%
Negative predictive value	77.6%	74.7%-80.6%
Accuracy	67.8%	64.6%-70.9%
F1 score	30.8%	-
F2 score	29.7%	-

CI: Confidence interval.

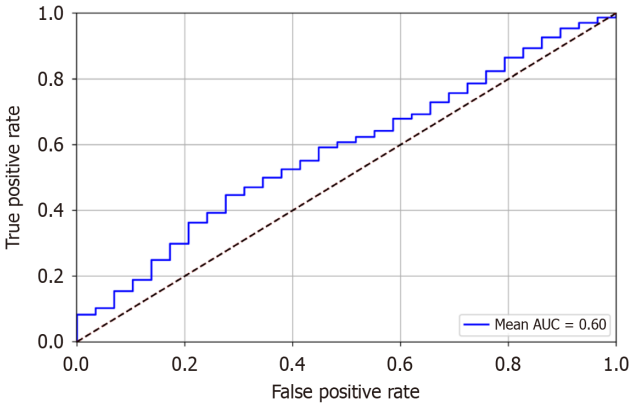


Figure 1 A graph illustrating the receiver operating characteristic curve and area under the curve. AUC: Area under the curve.

CONCLUSION

This study represents the first attempt to predict which patients will benefit from intra-articular corticosteroid injections using a LDA model. The moderate discriminative ability of the model, secondary to the heterogeneity in data reporting, underscores a need for a larger and more refined training dataset. Albeit, despite the limitations, our model can serve as a valuable reference, paving the way for future research to build upon our findings.

FOOTNOTES

Author contributions: Musbahi O, Cobb JP, and Jones GG conceptualized the study and designed the research methodology; Musbahi O, Pouris K, and Hadjixenophontos S curated the data; Musbahi O and Hadjixenophontos S analyzed the data; Musbahi O, Hadjixenophontos S, and Al-Saadawi A authored the manuscript; Musbahi O, Pouris K, Hadjixenophontos S, Al-Saadawi A, Soteriou I, Cobb JP, and Jones GG were involved in manuscript editing; Cobb JP and Jones GG were involved in supervision; and all authors thoroughly reviewed and endorsed the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Prognostic significance of hyponatremia in peripartum cardiomyopathy

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Abstract

BACKGROUND

Hyponatremia is the most common electrolyte imbalance, however the prognostic significance of hyponatremia in peripartum cardiomyopathy (PPCM) remains unclear.

AIM

To assess the prognostic significance of hyponatremia in PPCM patients.

METHODS

We consecutively recruited patients with PPCM from 14 sites in Nigeria and followed them up for a median of 18 months. Serum sodium was measured at baseline, and patients with hyponatremia (< 135 mmol/L) were compared with those with normal sodium levels. Cox proportional hazards regression models were developed to identify factors associated with all-cause mortality.

RESULTS
Of the 191 PPCM patients recruited, 90 (47.1%) had hyponatremia at presentation. All-cause mortality among the hyponatremic patients (24/90; 26.7%) was significantly higher than among patients with normal serum sodium (7/101; 6.9%) (*P*-value < 0.001). In the Cox proportional hazards regression model, hyponatremia was independently associated with an increased risk of all-cause mortality [hazard ratio: 3.18 (95% confidence interval: 1.35-7.52; *P* = 0.008)], as were hypotension (systolic blood pressure < 100 mmHg) [2.22 (1.03-4.79); *P* = 0.043] and left ventricular ejection fraction (LVEF) < 25% [3.14 (1.47-6.73), *P* = 0.003].

CONCLUSION
Hyponatremia was common in our cohort of PPCM patients, and was independently associated with a threefold increased risk for all-cause mortality. Hypotension and a LVEF below 25% at presentation were also independent predictors of mortality.

Key Words: Peripartum cardiomyopathy; Hyponatremia; Outcomes: PEACE registry

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Core Tip: Hyponatremia was common in our cohort of peripartum cardiomyopathy (PPCM) patients, and independently associated with threefold increased risk for all-cause mortality. Hypotension and a left ventricular ejection fraction below 25% at presentation were also independently associated with mortality. Our findings suggest that presence of hyponatraemia in PPCM patients at admission should prompt a thorough clinical evaluation and close clinical monitoring, to identify and address factors contributing to increased mortality risk.

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INTRODUCTION

Hyponatremia is the most common electrolyte imbalance, occuring in 10%-30% of hospitalized heart failure (HF) patients [1]. It is a well-described independent predictor of poor prognosis for both hospitalised and ambulatory HF patients[2]. Importantly, the reversal of the hyponatremia in HF is associated with improved survival[1]. Hyponatremia in HF can be either dilutional, which is more common and results from excessive neurohumoral upregulation leading to impaired water excretion, or depletional, which is primarily due to excessive natriuresis with the use of loop diuretics, or a combination of both mechanisms[3]. Hyponatremia is a strong predictor of mortality among HF patients, but it is unclear whether it has a direct effect on mortality or is only a marker of HF severity[1,2].

Peripartum cardiomyopathy (PPCM) is an important cause of HF among women in northern Nigeria and many other parts of the world, with an incidence as high as 1 in 96 live births, and maternal age < 20 years, hypotension, tachycardia, and left ventricular ejection fraction (LVEF) < 25% at baseline independently predicted mortality[4,5]. However, the prognostic significance of hyponatremia in PPCM is unknown. In this post-hoc analysis of PEACE (PPCM in Nigeria) registry data, we aimed to determine the prognostic significance of hyponatremia in PPCM patients. We hypothesised that hyponatremia would be associated with worse prognosis in PPCM patients.

MATERIALS AND METHODS

In the PEACE registry, PPCM patients were consecutively recruited from 14 sites across the geopolitical regions of Nigeria, and followed for a median of 18 months. The details of the study protocol have been previously published[6]. All data and supporting materials are available with the published article. PPCM patients were enrolled into the study after obtaining written informed consent, if they had HF symptoms and LVEF below 45%. Ethical approval for the study was obtained from the Research Ethics Committees of all the participating centres before the commencement of the study[6]. The study conformed to the ethical guidelines of the Declaration of Helsinki on the principles of medical research involving human subjects[7].

Serum sodium was measured at baseline using standard methods at the study sites, and patients with hyponatremia (< 135 mmol/L) were compared with those with normal values[8]. Unrecovered left ventricular (LV) systolic function was defined as LVEF ≤ 55% at the last follow-up.

Investigators were encouraged to prescribe standard and locally available HF drug therapies. These included a diuretic, beta-blocker, angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker or nitrate-

hydralazine combination, and a mineralocorticoid receptor antagonist, unless such use was contraindicated or resulted in unacceptable side effects. In addition, drug doses were individually tailored, in accordance with guideline recommendations[9].

Statistical analysis

Data was cleaned then summarised using standard statistical methods including mean (± SD), and proportions. Patients were classified into two groups (hyponatremic *vs* normal sodium levels) and compared based on baseline and last follow-up characteristics of interest. χ^2, Fisher's exact test, and student's *t* and Mann-Whitney tests were used to compare categorical and continuous variables, as appropriate. Mortality (occurring from baseline profiling to end of follow-up) was analysed in all 191 cases with complete follow-up using the Kaplan-Meier method followed by a Cox proportional hazards model (entry method with proportional hazards confirmed by visual inspection) to derive adjusted hazard ratios (HR) and 95% confidence interval (95%CI), with consideration of baseline demographic and clinical characteristics as independent correlates of all-cause mortality. Variables included in the model have been previously linked with increased risk for either mortality or hyponatremia in PPCM and HF patients[2,5]. A two-sided *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using "Statistical Package for Social Sciences" version 23.0 software.

RESULTS

A total of 191 PPCM patients were recruited from 14 sites across five out of the six geopolitical regions of Nigeria (155 patients from North-West, 17 patients from North-Central, 15 patients from South-West, 1 patient from South-East and 3 patients from South-South).

Overall, 90 of the 191 (47.1%) PPCM patients had hyponatremia at presentation. The clinical characteristics and prescriptions for diuretics and other HF drugs were well-balanced between the 2 groups; with and without hyponatremia (Table 1). None of the patients in both groups reported history of smoking and diabetes mellitus, and only one patient in each group reported alcohol intake. In addition,16.7% and 15.8% of the patients with and without hyponatremia respectively (*P* = 0.877) were recruited as in-patients.

All-cause mortality among the hyponatremic patients (26.7%) was significantly higher than among patients with normal serum sodium (6.9%) (*P* value < 0.001) (Table 2; Figure 1). The risk for all-cause mortality was independently increased by hyponatremia (HR 3.2; 95%CI: 1.4-7.5; *P*-value = 0.008), hypotension (systolic blood pressure < 100 mmHg) [HR 2.2 (95%CI: 1.0-4.8); *P* = 0.043], and LVEF < 25% [HR 3.1 (95%CI: 1.5-6.7); *P* = 0.003], after adjusting for loop diuretics (HR 1.1; *P* = 0.924), serum creatinine (HR 1.01; *P* = 0.425), preeclampsia (HR 0.8; *P* = 0.713) and tachycardia (HR 2.1; *P* = 0.130), at presentation respectively. Majority of the patients did not recover LV systolic function and rehospitalization was uncommon in both groups.

The paper was written according to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) Statement-checklist of items for cohort studies.

DISCUSSION

This study has shown, perhaps for the first time in PPCM patients, that hyponatremia at presentation was common and independently associated with threefold higher risk of all-cause mortality. The risk for mortality was also independently increased by hypotension and LVEF < 25% at baseline. It was however not associated with rehospitalisation and unrecovered LV systolic function. The LV systolic function in both groups still improved by 13-14%, irrespective of the hyponatremia status, in keeping with the natural history of PPCM. Thus, PPCM patients presenting with a combination of hyponatremia, hypotension and LVEF < 25% are at significantly high risk of short-term mortality, thus should be closely monitored and referred early to a specialized centre.

The prevalence of hyponatraemia in our study (47.1%) is higher than what was found in the European Society of Cardiology (ESC) HF long-term registry (20%) among patients hospitalized for acute HF[1]. In this retrospective analysis of the ESC Registry data, hyponatraemia at admission, defined as serum sodium concentration < 135 mmol/L, was associated with more advanced HF and worse in-hospital and post-discharge outcomes[1]. Importantly, HF patients with persisting hyponatraemia throughout admission had the highest in-hospital mortality as well as worst post-discharge outcomes, with all-cause mortality 60% higher than the reference group[1].

The prevalence of hyponatremia among HF patients of mixed aetiology admitted to a tertiary-level hospital in Ethiopia was lower than our finding among PPCM patients (28.9% *vs* 47.1% respectively)[10]. In that cohort, 49.3% were females and ischaemic heart disease was the predominant cause of HF (41%), followed by valvular heart disease (21%), hypertensive heart disease (17%) and dilated cardiomyopathy (11%). The lower prevalence of hyponatremia in this study was probably due to the lesser use of diuretics relative to our cohort (loop diuretics 29% *vs* 85%; spironolactone 9% *vs* 93%; thiazides 5% *vs* 1% respectively). However it is not clear whether PPCM has a predilection for hyponatremia.

In the Hyponatremia Registry for patients with euvolemic and hypervolemic hyponatremia in the United States, 29% of the HF patients had hyponatraemia. Unfortunately, the most commonly used treatment approaches for hyponatraemia in acute HF only increased serum sodium minimally, and most patients remained hyponatraemic at discharge[11].

Table 1 Clinical profile of peripartum cardiomyopathy patients with and without hyponatraemia, *n* (%)

Variables	Hyponatremia (*n* = 90)	Normal serum sodium (*n* = 101)	*P* value
Serum sodium, mmol/L	126.7 ± 22.3	139.9 ± 3.2	< 0.001
Age, years	28.5 ± 7.2	30.3 ± 7.2	0.086
NYHA II-IV	66 (73.3)	83 (82.2)	0.141
Unemployment	66 (73.3)	74 (73.3)	0.878
Uneducated	67 (74.4)	67 (66.3)	0.289
Multiparity	65 (72.2)	76 (75.3)	0.757
Twin pregnancy	18 (20.0)	13 (12.9)	0.256
Obesity	1 (1.1)	5 (5.0)	0.270
Stroke	3 (3.3)	1 (1.0)	0.344
History of preeclampsia	17 (18.9)	19 (18.8)	0.960
Systolic BP, mmHg	108 ± 16	110 ± 18	0.255
Diastolic BP, mmHg	74 ± 13	76 ± 15	0.233
Heart rate/min	100 ± 17	100 ± 19	0.789
Ascites	22 (24.4)	27 (26.7)	0.718
Left atrium, mm	45.4 ± 7.0	44.6 ± 6.7	0.465
LV end-diastolic dimension, mm	61.7 ± 9.2	62.5 ± 6.9	0.525
LV ejection fraction at baseline	30.1 ± 8.0	29.8 ± 7.4	0.777
LV ejection fraction at last follow-up	44.2 ± 12.7	42.5 ± 13.3	0.398
Serum creatinine, μmol/L	82.8 ± 29.3	82.5 ± 29.3	0.949
Heart failure treatment			
Loop diuretics	77 (85.6)	86 (85.2)	0.762
Thiazide diuretics	1 (1.1)	0	0.471
ACEI or ARB or BB	32 (35.6)	38 (37.6)	0.767
Spironolactone	84 (93.3)	94 (93.1)	0.942

Values were expressed as numbers with percentages in parentheses or as mean ± SD.
NYHA: New York Heart Association functional class; BP: Blood pressure; LV: Left ventricular; ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; BB: Beta-receptor blockers.

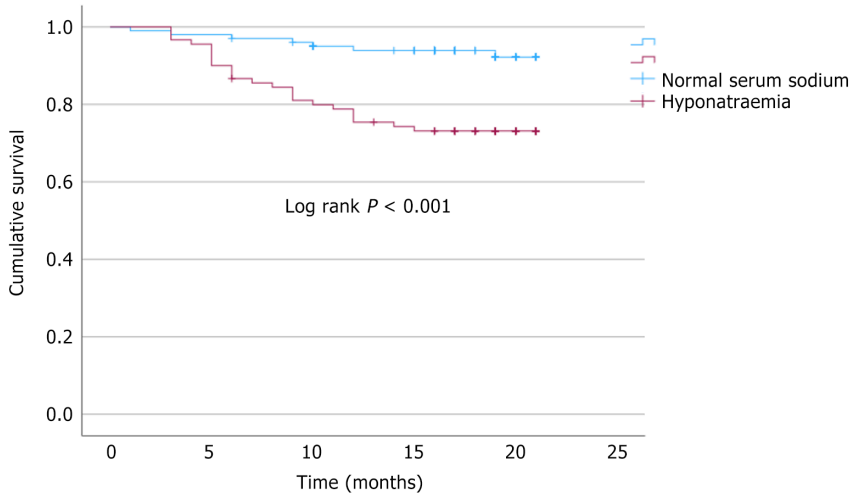
Table 2 Clinical outcomes among patients with and without hyponatraemia, *n* (%)

Variables	Hyponatremia (*n* = 90)	Normal serum sodium (*n* = 101)	*P* value
Mortality	24 (26.7)	7 (6.9)	< 0.001
Unrecovered left ventricular function	57 (63.3)	73 (72.3)	0.521
Rehospitalization	6 (6.7)	10 (9.9)	0.587

Values were expressed as numbers with percentages in parentheses.

Hyponatremia is considered a powerful independent marker of poor outcomes in patients with acute or chronic HF [12]. Given that hyponatraemia in HF is primarily dilutional, treatment is based on water restriction or vasopressin antagonists. Fluid should be restricted to less than 800-1000 mL/day to achieve a negative water balance and treat the hyponatraemia[12]. However, severe hyponatremia (£125 mmol/L) should be treated with intravenous hypertonic saline, targeting an increase in serum sodium of 1-2 mmol/L per hour, and ensuring that the increase is less than 8 mmol/L in a 24 hour period, to avoid the risk of myelinolysis[12].

Our results suggest that presence of hyponatraemia in PPCM patients at admission should prompt a thorough clinical evaluation and close clinical monitoring, to detect and treat the hyponatremia as well as other factors associated with



Number of patients at risk of mortality

Months	5	10	15	20
No hyponatraemia	98	94	82	38
Hyponatraemia	85	71	64	33

Figure 1 Kaplan-Meier survival curves showing patients with and without hyponatraemia at risk of mortality at each month of follow-up. Log rank (Mantel-Cox) $P < 0.001$.

increased risk of mortality. However, it is important to emphasise the post-hoc nature of our analysis and the overall pragmatic design of the PEACE registry; given the inherent challenges in optimally diagnosing and treating PPCM in an African setting.

CONCLUSION

Hyponatremia was common in our cohort of PPCM patients, and independently associated with 3-fold higher risk for all-cause mortality. Hypotension and LVEF below 25% at presentation were also independently associated with mortality.

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FOOTNOTES

Author contributions: Karaye KM conceptualised and designed the study, and acquired, analysed and interpreted data, drafted the article and revised it critically for important intellectual content, and approved the final submitted version. All other authors acquired, analysed and interpreted data, revised the article critically for important intellectual content, and approved the final submitted version. All authors read and approved the final manuscript.

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Observational Study

Knowledge, attitudes, and practice patterns regarding glaucoma among medical students and healthcare professionals in Eastern India

Bhagabat Nayak, Koyel Chakraborty, Shanmugasundaram Palanisamy, Ravikumar Subraya Rathod, Sucheta Parija, Bijnya Birajita Panda

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Abstract

BACKGROUND

Glaucoma is the leading cause of irreversible blindness worldwide, with 60.5 million affected individuals, of whom 11 million are from India. Due to its asymptomatic nature, the disease largely remains underdiagnosed or diagnosed in advanced stages, where little can be done to salvage functional vision. The literature suggests that a lack of knowledge is one of the reasons for its grave consequences. Assessment of awareness is the first step in planning management. Several studies have been conducted in the Indian community, but data from healthcare providers, who play a significant role in educating the masses directly or indirectly, are limited.

AIM

To identify awareness, knowledge, and attitudes about glaucoma among healthcare workers in a tertiary center in India.

METHODS

This cross-sectional study was conducted at a tertiary care institute in Eastern India. Data were collected from 423 participants by systematic stratified sampling after Institutional Ethics Committee approval *via* a pretested, self-designed,

semistructured, validated questionnaire. Statistical analyses were performed using the Statistical Package for Social Sciences Software v22.0. Continuous variables are expressed as the means ± SD for parametric values and medians with interquartile ranges for nonparametric values. The associations between the variables were studied *via* multivariate linear and logistic regression. $P < 0.05$ was considered statistically significant.

RESULTS

Most respondents were 20–30 years old ($n = 345$, 81.6%). The knowledge regarding glaucoma was good, and almost 56.3% of the participants gained knowledge from their medical training. The majority were aware that it has a familial predisposition and is secondary to high intraocular pressure, leading to irreversible peripheral vision loss. Only 42% knew about the life-long requirements of treatment. The resident group scored highest on knowledge- and attitude-based questions, whereas the faculty group scored highest on practice-based questions. Although 62% of the nursing staff had good attitude scores, their knowledge and practice scores were lower. The occupation group response difference was statistically significant ($P < 0.05$) for all the knowledge-based questions.

CONCLUSION

Although the majority of healthcare providers are aware of glaucoma, there is a dearth of knowledge about treatment modalities. Education *via* seminars and media can improve their knowledge, attitudes, and practices.

Key Words: Glaucoma awareness; Knowledge; Healthcare providers; Treatment modalities

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Core Tip: Our study aims to understand the current knowledge, attitude, practice, and awareness level among healthcare professionals decades after the worldwide awareness program on glaucoma, such as the World Glaucoma Week celebration. We are surprised that healthcare workers still lack awareness of glaucoma. Although the attitude shown was enthusiastic, many professionals require repeated seminars and awareness programs to enhance healthcare professionals' knowledge and practice patterns to increase their awareness in the community.

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INTRODUCTION

Glaucoma is characterized by a group of ocular conditions with progressive, irreversible optic nerve damage presenting specific optic disc features and visual field defect patterns[1-3]. The disease remains underdiagnosed among the public (nearly 75%), especially in developing countries, due to a lack of awareness[1,2] and the asymptomatic nature of the disease, especially with fewer follow-up visits[3,4]. Among all causes of blindness, glaucoma is the second most preventable cause, and intraocular pressure (IOP) is a modifiable risk factor[1,2,4,5]. In 2010, nearly 60.5 million people worldwide had glaucoma, which is expected to increase to 111.8 million by 2040[6,7]. Glaucoma not only causes blindness but also interferes with day-to-day activities, affecting the economy and quality of life[1].

Previous studies regarding the awareness of glaucoma among patients have shown that half of them were unaware of their condition at the time of diagnosis and hence presented with an advanced stage of the disease[8]. A community-based study in Nigeria highlighted the importance of community outreach programs with regular screening and patient education in primary health care[9]. A cross-sectional study conducted at Lome reported that 92.3% of healthcare professionals were aware of the grave consequences of glaucoma[3]. Another similar study in northern India reported that most (80.7%) physicians knew about the disease, and 24% were unaware of its familial predisposition[2]. A significant lacuna in the knowledge and awareness of glaucoma among healthcare professionals in Eastern India justifies the study.

MATERIALS AND METHODS

Aim

To assess glaucoma awareness among healthcare workers in a tertiary care hospital.

Objective

Comparative analysis of knowledge, attitudes, and practice patterns among health care workers in a tertiary hospital regarding glaucoma. The Department of Ophthalmology conducted this hospital-based cross-sectional study at the All

Table 1 Sociodemographic profile of the study participants, *n* (%)

	Nursing students (*n* = 50)	MBBS students (*n* = 122)	Resident doctors (*n* = 40)	Consultant (*n* = 40)	Nursing officer (*n* = 161)	Paramedical staff (*n* = 10)	Total (*n* = 423)
Age group							
20-30 years	50 (100)	122 (100)	35(87.5)	0 (0)	137 (85.0)	1 (10)	345 (81.6)
31-40 years	0 (0)	0 (0.0)	5 (12.5)	14 (35.0)	24 (15.0)	9 (90)	52 (12.3)
41-50 years	0 (0)	0 (0.0)	0 (0.00)	26 (65.0)	0 (0.0)	0	26 (6.1)
51-60 years	0 (0)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.0)	0	0 (0)
Sex							
Male	0 (0)	85(69.7)	21 (52.5)	34 (85.0)	42 (26.1)	1 (10.0)	183 (43.3)
Female	50 (100)	37 (30.3)	19 (47.5)	6 (15.0)	119 (74.9)	9 (90.0)	240 (56.7)

India Institute of Medical Sciences (AIIMS, Bhubaneswar; Odisha, India). All health care workers and staff working at AIIMS, Bhubaneswar, except health care workers in ophthalmology, were included in this study.

Study design: Hospital-based cross-sectional study.

Study setting: Department of Ophthalmology, AIIMS, Bhubaneswar.

Study participants: All health care workers and staff working at AIIMS, Bhubaneswar.

Study participant criteria: Inclusion criterion was participants working at this institution. Exclusion criteria were participants who were not willing to participate in the study and healthcare workers in the Department of Ophthalmology.

In a previous study performed at a tertiary care institute in northern India, 47.1% of the participants reported that high IOP causes optic nerve damage, leading to glaucoma[2]. An absolute error of 5%, with 95% confidence and a nonresponse rate of 10%, was considered. The minimum sample size required was 422 participants. As mentioned in the study instrument, systematic stratified sampling of equal samples from each stratum (job profile) was considered.

The sample size was calculated with the formula ($N = [Z_((1-\alpha) \times (PQ/d)])^2$, where N = minimum sample size needed, Z_((1-α)) = 1.96 considering an α error of 0.05 (95% confidence), P = knowledge related to glaucoma was assumed to be 47.1% (7), and Q = (1-P), d = error of 2.5 points, was considered acceptable.

After written informed consent was obtained from the study participants, a pretested, self-designed semistructured questionnaire was used for data collection. The questionnaire was translated into the local vernacular language (Odia) and back-translated to retain the original intended meaning. The questionnaire had two parts. Part A included all of the demographic information such as age, sex, education status, and type of job. Part B included questions on awareness, knowledge, and attitudes, which were asked of all health professionals. For awareness about glaucoma, the first question was "Have you ever heard of glaucoma?". If the answer was "No", the participant was considered unaware of glaucoma, and further questions about knowledge and attitudes were not asked. However, if the answer was "Yes", another question was asked about the participant's awareness of glaucoma and his/her ideas. Hearing the term "glaucoma" was not considered, as the participant was aware of glaucoma if he/she could not answer the second question on awareness. Then questions concerning knowledge and attitudes were further asked.

Statistical analyses

Data were collected using a pretested, self-designed semistructured questionnaire. Statistical analyses were performed using the Statistical Package for Social Sciences Software (SPSS) version 22.0 (IBM SPSS Statistics, Armonk, NY, United States). Continuous variables are expressed as the means ± SD for parametric values and medians with interquartile ranges for nonparametric values. The categorical variables are expressed as percentages or proportions. Associations between the variables were determined with appropriate statistical tests of significance. $P < 0.05$ was considered statistically significant.

RESULTS

There were 423 participants in this study, namely, 183 (43.3%) males and 240 (56.7%) females at a proportion of 1:1.3. Only 50 nursing students, 100% of whom were females, participated. The majority (81.6%) of respondents were young (20-30 years; *n* = 345, 81.6%) and were mostly students and nursing officers, as described in Table 1.

Knowledge regarding glaucoma was good among all groups. Most of the participants (95.2%) were aware of glaucoma. Almost 56.3% of the participants gained knowledge about glaucoma *via* medical training. Among the participants, 210

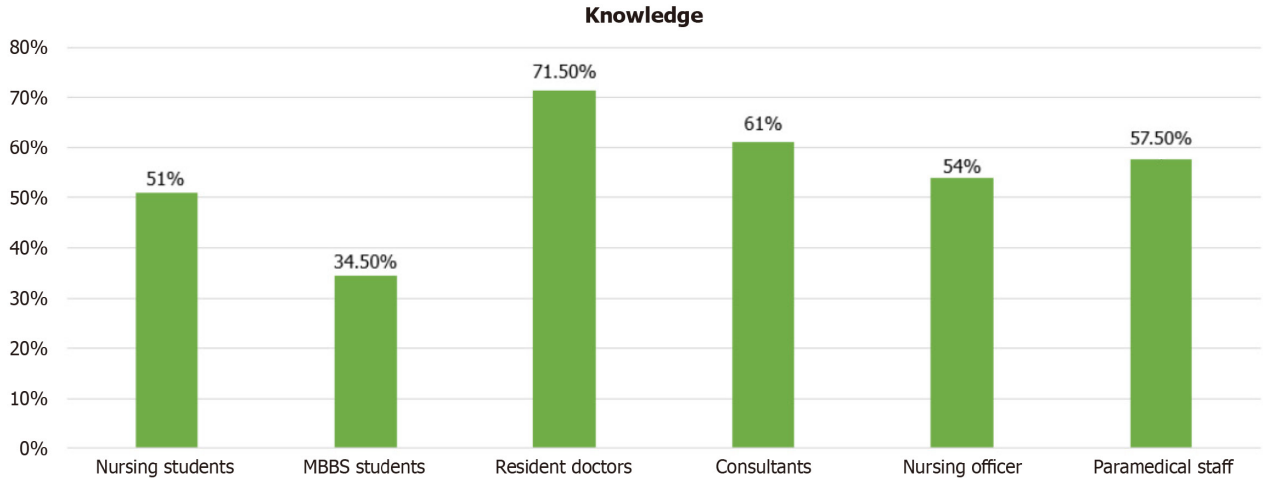


Figure 1 Column graph representation of the overall knowledge among the participants.

(49.6%) were aware of World Glaucoma Week celebration. Most of the participants were aware that high IOP causes blindness. Among all of the participants, resident doctors had more knowledge about glaucoma. The responses to knowledge-based questions were compiled, and the difference between the occupation groups was statistically significant ($P < 0.05$) for all five questions (Table 2).

In the attitude-based questionnaire, very few participants (11.1%) considered cataracts and glaucoma to be the same. Most participants were well aware of the risk factors for glaucoma. Almost all participants in the consultant group (100%) knew that early blindness from glaucoma was preventable. Most nursing staff (84.4%) knew that peripheral vision loss occurs in patients with glaucoma. Most of the participants were aware of the increased IOP associated with glaucoma. Overall, there were various responses in a part of the eye affected in patients with glaucoma. Nearly 48% of participants were aware of the familial predisposition of glaucoma. Among the participants, 51% were aware of the irreversible damage. In the treatment of glaucoma, only 11% of participants were mindful of device implant surgeries and laser treatment (32%), and 6% were not aware of any of the treatment modalities. Approximately 42% of the participants were aware of the lifelong requirements of medications and treatment. Thirty-nine percent of the participants reported that eye donation is required to treat glaucoma. Regarding glaucoma treatment, 76% answered that it would restore vision and delay progression (39%) (Table 3).

Among the participants, 16% had never undergone ophthalmological evaluation. Nearly 52% of the participants had visited an ophthalmologist in less than 1 year, and 47% strongly agree with routine yearly eye checkups. If the participants were diagnosed with glaucoma, 81% wanted to proceed with surgical treatment, and 17% preferred medical treatment. Only 14% of the participants had previously participated in glaucoma seminars, and 94% of the participants were in favor of awareness programs such as seminars (22%), regular TV (26%), regular FM (radio) (8%), articles (10%), brochures (8%), and all of these (54%) (Table 4).

Analysis of the knowledge-based responses of the various participants revealed that the resident doctor group had more knowledge (71.50%) than the other groups. The consultant group had the second highest percentage (61%), and the MBBS group had the lowest percentage (34.50%) (Figure 1).

According to the results of the attitude questionnaire, approximately 71.80% of the resident doctors responded well, 65% of the consultant group responded the least, and 43% of the MBBS students responded the least (Figure 2).

Analysis of the practice-based questionnaires among all the participants showed that the consultant group (53%) responded better than the resident doctors (45%), nursing officers (46%), and MBBS students (42%) (Figure 3).

DISCUSSION

In our study, there were 423 participants with a male:female ratio of 1:1.3, which correlates with the findings of a previous study by Amedome *et al*[3] that reported a similar proportion (1:1.04). Nevertheless, a study by Ichhpujani *et al* [2] reported a proportion of healthcare professionals of 1:2.5. The majority of studies involving healthcare workers reported that more than 90% of participants were aware of glaucoma [our study (95.2%) *vs* Ichhpujani *et al*[2] (100%) *vs* Amedome *et al*[3] (98.2%) *vs* Komolafeet *et al*[4] (100%)]. Nearly 56.2% of the participants in this study mentioned that they gained their glaucoma knowledge during medical training, whereas Ichhpujani *et al*[2] reported 78.9% (56.2% *vs* 78.9%).

Although the participants belonged to the medical community, 19 (4.8%) had not heard about glaucoma; however, a previous survey among healthcare professionals reported that more than 98% knew about glaucoma. Among the remaining participants who had heard about glaucoma, 26 (6%) participants did not know whether their family members were affected by it. In this study, 219 (51.7%) participants did not know the familial predisposition of the disease, and 71 (16.7%) had never had an ophthalmological evaluation. However, almost 91.2% of the participants opted for routine eye

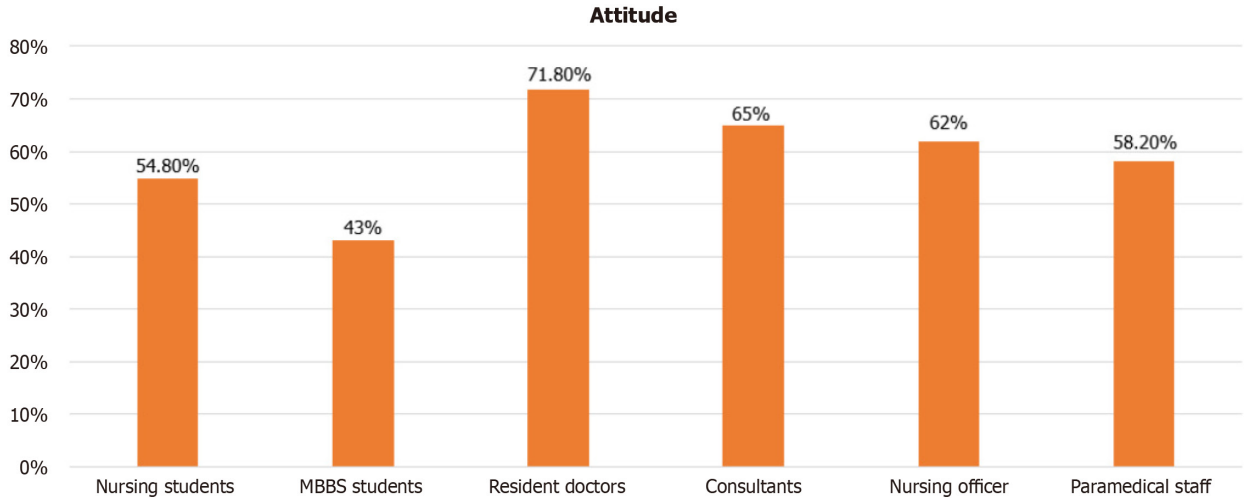


Figure 2 Column graph representation of the overall attitudes of the participants.

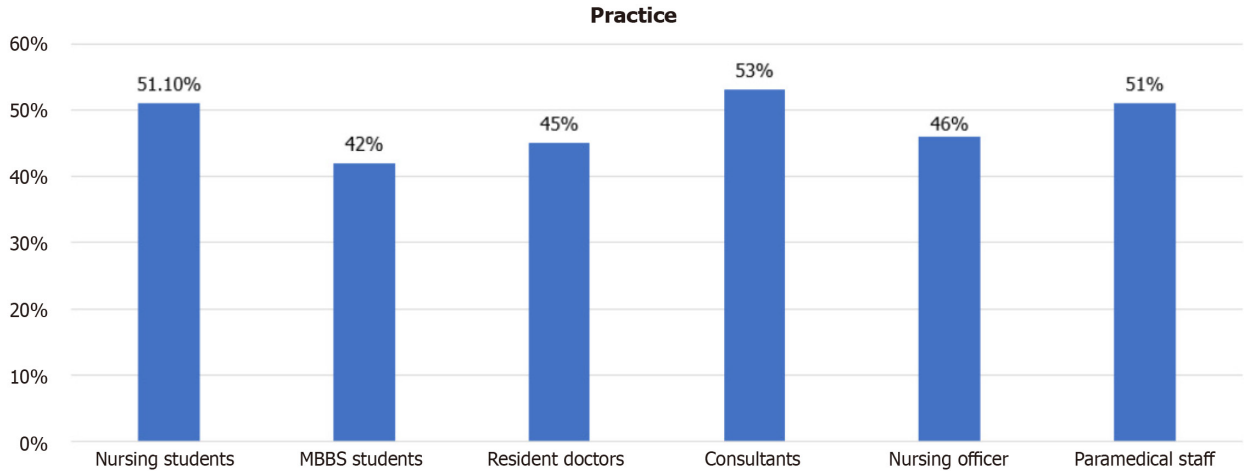


Figure 3 Column graph representation of the overall practices among the participants.

checkups. Twenty-three (5%) participants did not know that cataracts and glaucoma are separate entities, although a few had heard about glaucoma. Regarding the responses to the treatment-related questionnaires, 246 (58.1%) participants did not know about lifelong medication requirements such as those for systemic diseases. Although early diagnosis and treatment can prevent vision loss in these patients, 94 (22.2%) did not know about the early prevention of vision loss in patients with glaucoma. In addition, some of the participants had misinformation regarding eye donation, and 113 (26.71%) participants considered eye donation as a part of treatment. Half of the participants were unaware of the permanent vision damage associated with glaucoma, and 216 (51%) participants responded that therapy is intended to restore vision. In the advanced disease stage, when surgery is the only option, 17% of participants still preferred to continue with medication rather than surgery, and 4% opted for an alternative such as Ayurveda therapy.

The participants' responses to the practice pattern questionnaires were quite enthusiastic. Approximately 48.9% of the participants had not heard about World Glaucoma Week celebration, 85.5% had not attended any symposiums or seminars, 94.7% strongly supported glaucoma awareness programs, and 91.2% strongly agreed with routine eye checkups.

In a survey conducted in the rural population of North India, higher educational status, employed participants, and annual eye checkups were significantly positively associated with awareness of glaucoma[10]. Healthcare professionals are responsible for educating the public. A survey of Southeast Nigerian patients with diagnosed glaucoma (n = 95) reported that 68.5% did not know about familial predispositions and that 87% had poor attitudes[11]. Another survey among Southwest Nigerian people (n = 259) revealed that only 41 (15.8%) had heard about glaucoma, 21 (51.2%) of whom were physicians[12]. In our study, the source of information was medical training for almost 56% of the participants, followed by physician visits for 26% of the participants, similar to a previous study by Prabhu *et al*[13], in which physicians were the significant sources of information. In addition to physicians, nursing healthcare professionals also play a significant role in awareness campaigns. Even though all participants in our study had heard about glaucoma, their overall knowledge (51% and 54%), attitudes (54.8% and 58.2%), and practices (51.1% and 51%) were fair among the nursing students and nursing staff, similar to the findings of a study by Shetty *et al*[14], which was conducted among

Table 2 Response to knowledge-based questions, *n* (%)

	Nursing students (*n* = 50)	MBBS students (*n* = 122)	Resident doctors (*n* = 40)	Consultants (*n* = 40)	Nursing staff (*n* = 161)	Paramedical staff (*n* = 10)	*P* value
Q1. Have you heard about glaucoma?							
Yes	50 (100)	106 (86.9)	38 (95.0)	40(100)	160 (99.4)	9 (90.0)	< 0.001[1]
No	0 (0)	16 (13.1)	2 (5.0)	0 (0)	1(0.6)	1 (10.0)	
Q2. How do you explain glaucoma?							
High eye pressure	13 (26)	25 (20.4)	21 (52.5)	25 (62.5)	68 (42.2)	2 (20)	< 0.001[1]
High pressure causing blindness	26 (52)	54 (44.2)	17 (42.5)	27 (67.5)	85 (52.8)	6 (60)	
Damage to the eye nerve	9 (18)	30 (24.5)	27 (67.5)	10 (25)	37 (22.9)	1 (10)	
Causes visual field loss	1 (2)	11 (9)	22 (55)	10 (25)	34 (21.1)	0	
Others			0	0	3 (1)	1 (10)	
Q3. How did you learn about glaucoma?							
Mass media	2 (4)	12 (9.8)	1 (2.5)	0	4 (2)	0	< 0.001[1]
Friend	3 (6)	33 (27)	1 (2.5)	2 (5)	10 (6.2)	0	
Doctor	12 (24)	36 (29.5)	10 (25)	14 (35)	29 (18)	2 (20)	
Medical training	32 (64)	17 (13.9)	28 (70)	26 (65)	128 (79.5)	7 (70)	
Brochure	0 (0)	3 (2)	0	0	0	0	
Others	1 (2)	4 (2.2)	0	0	0	1 (10)	
Q4. Does anyone in your family have glaucoma?							
Yes	5 (10)	7 (5)	3 (7.5)	2 (5)	5 (3)	1 (10)	0.01[1]
No	43 (86)	97 (79.5)	34 (85)	36 (90)	153 (95.5)	8 (80)	
Do not know	2 (4)	16 (13.1)	3 (7.5)	2 (5)	2 (1.5)	1 (10)	
Q5. Have you heard about the World Glaucoma Week celebration?							
Yes	30 (60)	15 (12.5)	27 (67.5)	26 (65)	104 (64.5)	8 (80)	< 0.001[1]
No	20 (40)	105 (87.5)	13 (32.5)	14 (35)	55 (35.5)	2 (20)	

[1]χ^2 test.

nursing students in their final year. A survey by Ogbonnaya *et al*[15] in a rural Nigerian community revealed that the majority of participants (78.9%) had never heard of glaucoma, and those who heard about it received information from mass media. Hence, healthcare professionals must educate people about this vision-threatening condition *via* health campaigns. A survey of the North Indian population (*n* = 5000) by Rewri *et al*[16] revealed that only 409 (8.3%) patients were aware of glaucoma.

The limitation of this study was that only a few paramedical staff (lab technicians and occupational therapy technicians) were included. This was a cross-sectional study conducted at only one center in Eastern India, and almost one-third (*n* = 122, 28.8%) of the participants were MBBS students, which might have caused bias in the response.

CONCLUSION

Several studies have shown poor knowledge, attitudes, and practices toward glaucoma disease among the general population and even in patients with glaucoma. Healthcare professionals must educate the general public regarding the symptoms and signs of glaucoma. Not only ophthalmologists but also general physicians, nursing staff, and other healthcare workers can inform the public about glaucoma. Although less than half (49.6%) of our study population were aware of the World Glaucoma Week celebration, the majority (94.7%) strongly favored glaucoma awareness programs, and 91.2% opted for regular eye checkups. Ophthalmic healthcare workers can spread awareness about vision-threatening conditions among healthcare professionals and the community by utilizing awareness programs and

Table 3 Response to attitude-based questions, *n* (%)

	Nursing students (*n* = 50)	MBBS students (*n* = 122)	Resident doctors (*n* = 40)	Consultants (*n* = 40)	Nursing staff (*n* = 161)	Paramedical staff (*n* = 10)	*P* value
Q1. Glaucoma and cataracts are the same.							
Yes	3 (6)	0	1 (2.5)	0	5 (3.1)	0	< 0.01[1]
No	46 (92)	104 (85.2)	37 (92.5)	40 (100)	155 (96.2)	9 (90)	
Do not know	1 (2)	18 (14.8)	2 (5)	0	1 (0.6)	1 (10)	
Q2. Glaucoma occurs without symptoms.							
Yes	8 (16)	20 (16.4)	25 (62.5)	26 (65)	45 (27.9)	1 (10)	< 0.01[1]
No	38 (76)	48 (39.3)	13 (32.5)	14 (35)	113 (70.1)	7 (70)	
Do not know	4 (8)	54 (44.3)	2 (5)	0	3 (1.8)	2 (20)	
Q3. Risk factors for glaucoma.							
High BP	18 (36)	53 (42.5)	20 (50)	10 (25)	87 (54)	1 (10)	< 0.01[1]
Old age	26 (52)	31 (24.7)	18 (45)	9 (22.5)	82 (50.9)	4 (40)	
Family history	13 (26)	25 (21.5)	25 (62.5)	8 (20)	40 (24.8)	4 (40)	
Steroid use	7 (14)	6 (4.7)	21 (52.5)	21 (52.5)	23 (14.2)	0	
Do not know	0	18 (14.8)	3 (7.5)	4 (10)	4 (2.4)	1 (10)	
Q4. Early blindness from glaucoma is preventable.							
Yes	38 (76)	65 (53.3)	37 (92.5)	40 (100)	140 (86.9)	9 (90)	< 0.01[1]
No	8 (16)	10 (8.2)	0	0	10 (6.2)	1 (10)	
Do not know	4 (8)	47 (36.9)	3 (7.5)	0	11 (6.8)	0	
Q5. Peripheral vision loss occurs in glaucoma.							
Yes	35 (70)	67 (54.9)	32 (80)	27 (67.5)	136 (84.4)	7 (70)	< 0.01[1]
No	8 (16)	6 (4.9)	3 (7.5)	2 (5)	10 (6.2)	3 (30)	
Do not know	7 (14)	49 (40.2)	5 (12.5)	11 (27.5)	15 (9.3)	0	
Q6. What happens to eye pressure in glaucoma?							
Increases	44 (88)	98 (80.3)	37 (92.5)	40 (100)	158 (98.1)	8 (80)	< 0.01[1]
Decreases	2 (4)	4 (3.3)	1 (2.5)	0	0	0	
Do not know	4 (8)	20 (16.3)	2 (5)	0	3 (1.8)	2 (20)	
Q7. Which part of the eye is affected?							
Cornea	11 (22)	22 (17.1)	6 (15)	6 (15)	33 (20.4)	6 (60)	< 0.01[1]
Lens	12 (24)	29 (22.6)	2 (5)	0	31 (19.2)	5 (50)	
Retina	8 (16)	34 (27.8)	11 (27.5)	22 (55)	45 (27.9)	3 (30)	
Optic nerve	29 (48)	51 (41.7)	36 (90)	24 (60)	113 (70.1)	8 (80)	
Others	0	0	0	0	2 (1.2)	0	
None	2 (4)	17 (13.9)	2 (5)	2 (5)	2 (1.2)	0	
Q8. If glaucoma is present in your family, can you develop it?							
Yes	31 (62)	39 (32)	34 (85)	25 (62.5)	69 (42.8)	6 (60)	< 0.01[1]
No	14 (28)	28 (23)	3 (7.5)	3 (7.5)	75 (46.5)	3 (30)	
Do not know	5 (10)	55 (44)	3 (7.5)	12 (30)	17 (10.5)	1 (10)	
Q9.Vision loss in glaucoma.							
Reversible	11 (22)	18 (14.8)	7 (17.5)	6 (15)	44 (27.3)	3 (30)	<

Irreversible	33 (66)	58 (47.5)	25 (62.5)	30 (75)	96 (59.6)	6 (60)	0.01[1]
Don't know	6 (12)	46 (37.7)	8 (20)	4 (10)	21 (13)	1 (10)	
Q10. Is a person with diabetes or hypertension at risk of glaucoma?							
Yes	41 (82)	71 (58.2)	36 (90)	31 (77.5)	154 (95.6)	8 (80)	< 0.01[1]
No	5 (10)	4 (3.3)	0	0	3 (1.8)	1 (10)	
Don't know	4 (8)	47 (38.5)	4 (10)	9 (22.5)	5 (3.1)	1 (10)	
Q11. Is glaucoma treatable?							
Yes	39 (78)	65 (53.3)	37 (92.5)	38 (95)	149 (92.5)	7 (70)	< 0.01[1]
No	7 (14)	17 (13.9)	1 (2.5)	2 (5)	8 (4.9)	2 (20)	
Do not know	4 (8)	37 (30.3)	2 (5)	0	4 (2.4)	1 (10)	
Q12. What treatments are available?							
Eyedrops	28 (56)	66 (53)	30 (75)	33 (82.5)	107 (66.4)	7 (70)	< 0.01[1]
Tablets	14 (26)	13 (10.5)	23 (57.5)	11 (27.5)	49 (30.3)	3 (30)	
Laser	13 (26)	33 (26.9)	25 (62.5)	12 (30)	49 (30.3)	4 (40)	
Surgery	36 (72)	64 (51)	32 (80)	14 (35)	140 (86.9)	8 (80)	
Device implant	1 (2)	5 (4)	23 (57.5)	0	20 (12.4)	0	
Others	2 (4)	0	0	0	1 (0.6)	0	
None	2 (4)	20 (16.4)	2 (5)	0	1 (0.6)	1 (10)	
Q13. Treatment is lifelong.							
Yes	20 (40)	31 (25.4)	19 (47.5)	13 (32.5)	87 (54.0)	7 (70)	< 0.01[1]
No	17 (34)	22 (18)	10 (25)	17 (42.5)	53 (32.9)	2 (20)	
Do not know	13 (26)	69 (54.9)	11 (27.5)	10 (25)	21 (13.0)	1 (10)	
Q14. It can be treated by eye donation.							
Yes	25 (50)	27 (22.1)	6 (15)	11 (27.5)	38 (23.6)	6 (60)	< 0.01[1]
No	15 (30)	34 (27.9)	25 (62.5)	21 (52.5)	86 (53.4)	1 (10)	
Do not know	10 (20)	61 (47.5)	9 (22.5)	8 (20)	37 (22.9)	3 (30)	
Q15. Purpose of treatment in glaucoma.							
Restore vision	32 (64)	39 (31.9)	16 (40)	22 (55)	103 (63.9)	4 (40)	< 0.01[1]
Delay progression	16 (32)	46 (37.7)	28 (70)	19 (47.5)	51 (31.6)	6 (60)	
Do not know	2 (4)	37 (30.1)	3 (7.5)	3 (7.5)	7 (4.3)	0	

[1]χ^2 test. BP: Blood pressure.

Table 4 Response to practice-based questions, *n* (%)

	Nursing students (*n* = 50)	MBBS students (*n* = 122)	Resident doctors (*n* = 40)	Consultants (*n* = 40)	Nursing staff (*n* = 161)	Paramedical staff (*n* = 10)	*P* value
Q1. When did you last visit an ophthalmologist?							
< 1 year	26 (52)	78 (64.7)	22 (55)	23 (57.5)	65 (40.3)	7 (70)	< 0.01[1]
1-2 years	14 (28)	14 (12.4)	8 (20)	13 (32.5)	21 (13.0)	2 (2)	
> 3 years	3 (6)	10 (8.2)	5 (12.5)	4 (10)	29 (18)	1 (10)	
Never	7 (14)	13 (10.7)	5 (12.5)	0	46 (28.5)	0	
Q2. Are you in favor of routine yearly eye checkups?							

Strongly agree	28 (56)	47 (38.5%)	22 (55%)	40 (100%)	57 (35.4)	5 (50)	< 0.01[1]
Agree	18 (36)	56 (45.9)	16 (40)	0	93 (57.5)	4 (40)	
Neutral	3 (6)	13 (10.7)	4 (10)	0	9 (5.5)	1 (10)	
Disagree	1 (2)	3 (2.5)	3 (7.5)	0	2 (12)	0	
Strongly disagree	0	3 (2.5)	0	0	0	0	
Q3. If you were diagnosed with glaucoma, would you agree to treatment?							
Visit your ophthalmologist regularly and take the suggested treatment	43 (86)	93 (76.2)	28 (70)	36 (90)	134 (83.2)	9 (90)	0.02[1]
Might miss one or two doses	3 (6)	2 (1.6)	5 (12.5)	0	4 (2.4)	0	
Will prefer getting glaucoma surgery	4 (8)	27 (22.1)	7 (17.5)	4 (10)	27 (16.7)	1 (10)	
Q4. If surgery was the only treatment option available, what would you do?							
Will promptly go ahead with the surgery	41 (82)	82 (67.2)	36 (90)	20 (50)	138 (85.7)	10 (100)	< 0.01[1]
Try to defer surgery and continue eye drops	7 (14)	29 (23.8)	1 (2.5)	20 (50)	15 (9.3)	0	
Take eyedrops and start alternatives like Ayurveda	2 (4)	11 (9)	3 (7.5)	0	3 (1.8)	0	
Q5. Have you attended any seminars or symposiums on glaucoma?							
Yes	12 (24)	11 (9)	6 (15)	9 (22.5)	20 (12.4)	3 (30)	0.047[1]
No	38 (76)	111 (91)	34 (85)	31 (77.5)	141 (87.5)	7 (70)	
Q6. Will you support the glaucoma awareness program and camps?							
Strongly agree	27 (54)	68 (55.7)	24 (60)	34 (85)	93 (57.7)	5 (50)	0.02[1]
Agree	21 (42)	42 (34.4)	15 (37.5)	4 (10)	64 (39.7)	4 (40)	
Neutral	2 (4)	10 (8.2)	1 (2.5)	0	4 (2.4)	1 (10)	
Disagree	0	0	0	0	0	0	
Strongly disagree	0	2 (1.6)	0	0	0	0	
Q7. Which type of awareness program do you think will reach more people and be more informative?							
Seminars	10 (20)	28 (22.9)	5 (5)	8 (20)	42 (26.1)	4 (40)	< 0.01[1]
Regular TV	11 (22)	32 (26.1)	15 (37.5)	8 (20)	43 (26.7)	3 (30)	
Regular FM	2 (4)	6 (4.8)	9 (22.5)	10 (25)	8 (4.9)	1 (10)	
Article	3 (6)	20 (16.4)	10 (25)	2 (5)	8 (4.9)	1 (10)	
Brochure	3 (6)	13 (7.2)	0	2 (5)	17 (10.5)	1 (10)	
Others	3 (6)	2 (1.6)	0	0	4 (2.4)	0	
All of the above	28 (56)	66 (53.1)	19 (47.5)	18 (45)	95 (59)	4 (40)	

[1]χ^2 test.

screening campaigns. For example, programs such as the World Glaucoma Week celebration, which is held worldwide in the second week of March every year, should be expanded to increase awareness among the public and healthcare workers.

FOOTNOTES

Author contributions: Bhagabat N designed and conducted the study; Koyel C and Shanmugasundaram P wrote the manuscript; Rathod RS contributed to the statistical analyses; Bhagabat N, Sucheta P, and Bijnya P provided clinical inputs and critically analyzed the manuscript; Bhagabat N supervised the study; Palanisamy S acquired the clinical data, prepared the first draft of the manuscript, prepared a datasheet, searched the literature, and was responsible for the preparation of figures; Panda BB critically analyzed the initial manuscript and provided crucial inputs that were essential for preparing the final version of the manuscript. The collaboration between

Panda BB and Palanisamy S helped in representing the figures correctly, formulating the discussion after proper literature review, and keeping up with the manuscript guidelines, which were essential for the final version of the manuscript.

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ORIGINAL ARTICLE

Observational Study

Analgesic efficacy of continuous ultrasound-guided unilateral erector spinae block and thoracic epidural analgesia in patients undergoing antero-lateral thoracotomy

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Abstract

BACKGROUND

Chest physiotherapy and incentive spirometry, essential for pulmonary care, can exacerbate acute post-thoracotomy pain. Pain relief is, therefore, essential to facilitate early mobilization. This study evaluated the analgesic efficacy of unilateral continuous erector spinae block (ESB) compared to thoracic epidural analgesia (TEA) in terms of quality of pain relief and perioperative hemodynamic changes.

AIM

To compare the analgesic efficacy of continuous ultrasound-guided unilateral ESB and thoracic epidural in patients undergoing antero-lateral thoracotomy.

METHODS

This prospective, observational study was conducted at a tertiary care hospital of central India. Sixty-eight adult patients of either gender, posted for elective thoracic surgeries requiring one lung ventilation, were allocated to either TEA (n = 34) or ESB (n = 34) group, based on the attending anesthesiologist's expertise. Continuous data were analyzed by independent t-tests, and categorical data by χ^2 tests.

RESULTS

The proportion of patients requiring rescue opioids within 24 hours post-

extubation was similar between the two group. Resting numerical rating scale scores (0 hour, 6 hours, and 72 hours post-extubation) were significantly higher in the ESB group compared to the TEA group [1.70 ± 1.03 *vs* 1.05 ± 0.77 (P = 0.004); 1.64 ± 0.98 *vs* 1.2 ± 0.88 (P = 0.05); 3.2 ± 1.07 *vs* 2.61 ± 0.92 (P = 0.013)]. Dynamic numerical rating scale scores and post-extubation mean arterial pressures were also higher in the ESB group. Additionally, block performance time was significantly longer in the ESB group (16.58 ± 3.66 *vs* 13.84 ± 2.88, P = 0.001).

CONCLUSION

The two techniques provided similar opioid-sparing effects following antero-lateral thoracotomy, though TEA exhibited a superior analgesic efficacy at the expense of increased hemodynamic instability requiring vasopressor support.

Key Words: Epidural analgesia; Erector spinae plane block; Opioid; Pain management; Postoperative pain; Thoracotomy; Ultrasonography

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Core Tip: This prospective study compared the analgesic efficacy of unilateral continuous erector spinae block (ESB) *vs* thoracic epidural analgesia (TEA) in patients undergoing thoracotomy, evaluating pain scores and perioperative hemodynamics. While rescue opioid requirements within 24 hours post-extubation were comparable between the two groups, resting numerical rating scale scores at 0 hour, 6 hours, and 72 hours were significantly higher in the ESB cohort. Hemodynamically, the ESB group maintained higher mean arterial pressures, whereas TEA was associated with greater hypotensive episodes, necessitating significantly more vasopressor support to sustain mean arterial pressures ≥ 65 mmHg at 0 hours and 6 hours. Although TEA demonstrates superior analgesia, its use is limited by increased hemodynamic instability, suggesting ESB as a viable alternative when cardiovascular compromise is a concern.

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INTRODUCTION

Thoracotomy is widely recognized as one of the most painful surgical procedures[1]. Acute post-thoracotomy pain is aggravated by the constant chest wall movement of breathing[1]. Despite this, chest physiotherapy and incentive spirometry are encouraged to prevent postoperative atelectasis and retention of secretions. Inadequate pain management can lead to complications such as pulmonary issues (atelectasis, pneumonia, retention of bronchial secretions), cardiovascular effects (tachycardia, increased oxygen consumption), and muscle weakness[2,3]. Pain relief is, therefore, crucial to facilitate coughing and deep breathing exercises and early mobilization.

The American Society of Anaesthesiology recommends multimodal perioperative pain management techniques[3]. Perioperative techniques for postoperative pain management include systemic opioids, peripheral regional analgesic techniques, and local anesthetic infiltration of incisions[3]. However, opioids can cause nausea, vomiting, pruritus, and respiratory depression, which may have detrimental effects on post-thoracotomy patients[4,5]. Various regional techniques such as thoracic epidural analgesia (TEA), paravertebral block, intercostal block, and intra-pleural analgesia have been widely used to manage post-thoracotomy pain[6-9]. While TEA remains the gold standard, it is associated with complications such as autonomic blockade and trauma to central neuraxial structures[10-12].

More recently, ultrasound-guided erector spinae block (ESB) has emerged as a promising technique for managing thoracic neuropathic pain, rib fractures, and postoperative pain following breast surgery[13]. This novel technique provides effective thoracic analgesia with a potentially safer profile than TEA or paravertebral blocks, as the injection site is farther from neurovascular structures and the pleura. Its efficacy in chronic thoracic pain management makes it an attractive alternative[14-16].

This study evaluated the analgesic efficacy of unilateral continuous ESB compared to TEA in terms of quality of pain relief and perioperative hemodynamic stability. By comparing these two regional analgesia techniques for post-thoracotomy pain, this study aimed to provide evidence for optimizing analgesic strategies.

The primary objective of this study was to compare the proportion of participants requiring rescue analgesia within 24 hours postoperatively. The secondary objectives included assessing static and dynamic pain scores at extubation, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, and 72 hours post-extubation, as well as evaluating postoperative hemodynamic instability between the two groups of patients undergoing antero-lateral thoracotomy.

MATERIALS AND METHODS

This prospective, observational study was conducted at All India Institute of Medical sciences, Bhopal, India between January 2022 to November 2022. The institutional ethics committee approval was obtained and registration of trial with the Clinical Trial Registry-India (vide registration number CTRI/2021/12/038993, https://www.ctri.nic.in) was done. Sixty-eight adult patients of either gender belonging to American Society of Anaesthesiology physical status class II or III, posted for elective thoracic surgeries requiring one lung ventilation, were included in the study. Written informed consent was obtained from all the participants for the procedure and participation in the study and to use their data for research and educational purposes. The study was conducted in accordance with the 2013 declaration of Helsinki, and the reporting of the study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Patients with anomalies of vertebral column, psychological disorders, or bleeding diathesis, on anti-coagulants, having blood or cerebro-spinal fluid tap during procedure, having opioid dependency or abuse, with a history of chronic pain on opioids, uncontrolled hypertension, or uncontrolled diabetes mellitus, and undergoing emergency surgery were excluded from the study.

Patients were allocated to either TEA (n = 34) or ESB (n = 34) group, based on the attending anesthesiologist's expertise using a convenience sampling method. The patients were shifted inside the operation theatre and standard monitoring (non-invasive blood pressure, electrocardiogram, and pulse oximetry) was established. A wide bore intravenous (IV) cannula was secured and IV fluids were started at 8 mL/kg/hour. Continuous hemodynamic monitoring with a radial artery catheterization was done intraoperatively and postoperatively.

In the TEA group, a thoracic epidural catheter was inserted at T5-T6 level with the patient in the sitting position, using a 16G Touhy needle. After confirming the epidural space by the loss of resistance technique, the epidural catheter was threaded 4 cm into the epidural space. In the ESB group, ultrasound (USG)-guided unilateral erector spine block was performed in the lateral position with a 16G Touhy needle at T5-T6 level. After hydro-dissection with normal saline, an epidural catheter was threaded 4 cm into the erector spinae space. In both groups, the catheter was secured with 24G "Lock-it plus" epidural catheter securing device. After securing the catheter, general anaesthesia was induced. Thereafter, the patient was placed in the supine position and a loading dose of local anaesthetic (10 mL of 0.25% bupivacaine) was injected into the desired space, followed by a continuous infusion of 0.125% plain bupivacaine at a rate of 5-7 mL/hour till 48 hours post-extubation, and adjusted based on the patient's numerical rating scale (NRS) pain scores.

General anaesthesia was induced with inj. glycopyrolate 4 mcg/kg, inj. midazolam 0.05 mg/kg, inj. fentanyl 2 mcg/kg, and inj. propofol 2-3 mg/kg IV. After confirming proper bag-mask ventilation, inj. vecuronium 0.1 mg/kg was administered to facilitate intubation. A disposable polyvinylchloride left-sided Robertshaw double-lumen tube was inserted. Correct placement of the double-lumen tube was confirmed by fibreoptic bronchoscopy and auscultation.

During one lung ventilation, all patients were ventilated with a tidal volume of 6 mL/kg with O_2, air, and isoflurane and with a positive end-expiratory pressure of 5 cm of water. FiO_2 was adjusted to maintain oxygen saturation up to 94% and respiratory rate was adjusted to keep the PCO_2 and pH in the acceptable clinical range. Intraoperative analgesia was maintained with inj. paracetamol 15-20 mg/kg and inj, fentanyl in aliquots of 0.5 mcg/kg every 60 minutes guided by the hemodynamic parameters. Any episode of hypotension (a fall in systolic blood pressure of 20% or more of the baseline), if any, was noted and treated with inj. phenylephrine 50 mcg, followed by infusion of inj. nor-adrenaline at 0.05-0.15 mcg/kg/minute, to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg. At the end of surgery, patients were extubated and shifted to Intensive Care Units for postoperative care.

Technique of ESB

In the ESB group, USG-guided unilateral (depending upon side of thoracotomy) erector spinae plane block was performed under all aseptic precautions, in lateral position. A linear array, high frequency probe (5-13 MHz) of USG system was placed in longitudinal plane 3 cm lateral to the T6 spinous process corresponding to the T5 transverse process. Three muscles, *i.e.*, the trapezius (uppermost), rhomboid major (middle), and erector spinae (lowermost), were identified superior to the hyper-echoic transverse process (Figure 1). Using in-plane approach, a 16 G Tuohy needle was inserted in caudal-cephalad direction, until the tip of needle was deep to the erector spinae muscle. Hydro-dissection below the muscle plane was done by injecting 5 mL of normal saline. An 18 G epidural catheter was then threaded 4 cm in cephalad direction.

Technique of TEA

In the TEA group, a thoracic epidural catheter was inserted under strict aseptic precautions, before induction of general anaesthesia. Local infiltration with 2% of lignocaine under the skin at T5-T6 intervertebral space was administered. An 18 G Tuohy needle was inserted at T5-T6 level to identify epidural space using loss of resistance technique. A 20 G catheter was threaded 4 cm in the epidural space.

A bolus dose of 10 mL of 0.25% plain bupivacaine was administered after induction followed by a continuous infusion of 0.125% plain bupivacaine at 5-7 mL/hour till 48 hours post-extubation in both the study groups. The pain assessment was performed using a 11-point NRS, *i.e.*, 0-10. The postoperative pain assessment was done at rest (static pain) and during spirometry (dynamic pain) using the 11-point NRS tool at 0 hour (extubation), 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, and 72 hours post-extubation. Respiratory efforts in the postoperative period were assessed by the number of balls raised in the spirometer, which indicates the peak inspiratory flow rate. In the postoperative period, a pain score of 4 or more on NRS at rest was defined as breakthrough pain[17]. IV paracetamol 1 gm every 6 hours was administered to patients in both the study groups. Rescue analgesia was administered, at NRS > 4 at rest or on patient's demand with inj. fentanyl 0.5 mcg/kg.

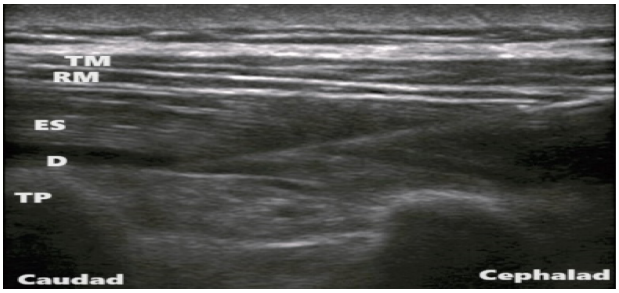


Figure 1 Sono-anatomy of erector spinae block. TM: Trapezius muscle; RM: Rhomboid major; ES: Erector spinae muscle; D: Drug (local anaesthetic) deposited deep to erector spinae muscle; TP: Transverse Process.

During the postoperative period, any episode of hypotension (a fall in systolic blood pressure of 20% or more of the baseline), if any, was noted and treated with inj. nor-adrenaline infusion to maintain a MAP of 65 mmHg or more.

The proportion of patients requiring rescue opioid within 24 hours postoperatively, episodes of hemodynamic instability, and any other complications associated with each block were compared between the two groups. The primary outcome of this study was to compare the proportion of participants requiring rescue analgesia within 24 hours postoperatively. The secondary outcomes were to assess the static and dynamic pain scores at extubation, post-extubation at 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, and 72 hours and any hemodynamic instability postoperatively between the two groups of patients undergoing antero-lateral thoracotomy.

Sample size calculation

Sakae *et al*[17] compared erector spinal plane block and epidural block techniques for postoperative analgesia for open cholecystectomies. They found that 43% of patients in the ESB group needed rescue opioid within 24 postoperative hours, whereas only 13% required the same in the TEA group. Using G × Power 3 software for Windows (University of Kiel, Kiel, Germany) for calculation of the sample size, and based on the differences in proportion of patients requiring rescue opioid within 24 hours postoperatively between the ESB and TEA groups in the study done by Sakae *et al*[17], a sample size of 34 participants in each group was required to achieve an alpha-error of 0.05 and with 80% as the power of study.

Data analyses were conducted using Statistical Package for the Social Sciences (International Business Machines Corporation, NY, United States) for Windows, version 21. The data analysts were blinded to group assignment. Variables including age, time taken to perform the block, breath holding time, pain scores, and MAP, presented as the mean ± SD, were compared using the independent Student's *t*-test. Categorical variables such as gender, balls lifted in spirometer, and proportion of participants requiring rescue opioids, expressed as numbers (%), were analyzed using the χ^2 test. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Seventy-two patients were assessed for eligibility (Figure 2). Demographic and baseline parameters, including the number of balls lifted in the spirometer and breath-holding time, were comparable between the two study groups (Table 1). The proportion of patients requiring rescue opioids within 24 hours post-extubation was similar between the two study groups (4/34 *vs* 4/34, *P* = 1) (Figure 3). The time taken to perform the block was significantly longer in the ESB group as compared to the TEA group (16.58 ± 3.66 *vs* 13.84 ± 2.88, *P* = 0.001) (Table 1). The resting NRS scores at 0 hours, 6 hours, and 72 hours post-extubation were significantly higher in the ESB group as compared to the TEA group (1.70 ± 1.03 *vs* 1.05 ± 0.77, *P* = 0.004, 1.64 ± 0.98 *vs* 1.20 ± 0.88, *P* = 0.050, and 3.20 ± 1.07 *vs* 2.61 ± 0.92, *P* = 0.013, respectively) (Table 2). A significantly higher dynamic NRS was observed throughout the postoperative period in the ESB group as compared to the TEA group (Table 2).

The proportion of patients lifting one ball in spirometer was significantly more in the ESB group at 6 hours (8/34 *vs* 1/34, *P* = 0.012), 12 hours (10/34 *vs* 1/34, *P* = 0.003), and 24 hours (6/34 *vs* 1/34, *P* = 0.045) post-extubation as compared to the TEA group. The proportion of patients lifting two balls in spirometer at 48 hours (18/34 *vs* 9/34, *P* = 0.025) and 72 hours (16/34 *vs* 6/34, *P* = 0.009) post-extubation was higher in the ESB group. The proportion of patients lifting three balls in spirometer was significantly higher in the TEA group at 6 hours (10/34 *vs* 22/34, *P* = 0.003), 12 hours (14/34 *vs* 26/34, *P* = 0.003), 24 hours (12/34 *vs* 24/34, *P* = 0.003), 36 hours (12/34 *vs* 21/34, *P* = 0.029), 48 hours (12/34 *vs* 24/34, *P* = 0.003), and 72 hours (14/34 *vs* 27/34, *P* = 0.001) post-extubation.

The post-extubation MAPs were significantly higher in the ESB group as compared to the TEA group, and the proportion of patients requiring inotropic support to maintain a MAP of 65 mmHg was significantly higher in the TEA group at 0 hours (14/34 *vs* 0/34, *P* = 0.001) and 6 (14/34 *vs* 2/34, *P* = 0.001) hours post-extubation (Table 3). Total nor-adrenaline used postoperatively was higher in the TEA group (3.61 ± 0.96) as compared to the ESB group (3.49 ± 1.51), but statistically insignificant (*P* = 0.680).

Table 1 Patient demographics, baseline lung function, block characteristics, and peri-operative drugs used in the study groups, mean ± SD

Parameter	ESB (*n* = 34)	TEA (*n* = 34)	*P* value
Age (year)	46.1 ± 11.28	47.08 ± 12.07	0.750
Gender (male:female)	20/14	24/10	0.310
Body mass index (kg/m^2)	24.7 ± 1.6	25.1 ± 1.8	0.520
ASA physical status (II/III)	28/6	31/3	0.280
Balls lifted in spirometry preoperatively (1/2/3)	15/14/5	10/18/6	0.450
BHT (seconds)	20.4 ± 2.04	20.35 ± 2.41	0.910
Time taken to perform the block (minutes)	16.58 ± 3.66	13.84 ± 2.88	0.001[a]
Type of surgery (lobectomy/ decortication/ pneumonectomy)	12/14/8	12/15/7	0.100
Intraoperative fentanyl consumed (mcg)	196.41 ± 5.68	195.07 ± 6.74	0.370
Intraoperative fluid administered (mL)	1469.35 ± 28.64	1481.05 ± 29.64	0.100
Intraoperative phenylephrine used (mcg)	0.950 ± 0.3985	1.139 ± 1.1853	0.380
Postoperative nor-adrenaline used (mg)	3.49 ± 1.51	3.61 ± 0.96	0.680

[a]*P* indicates significant value.
ESB: Erector spinae plane block; TEA: Thoracic epidural anaesthesia; ASA-PS: American Society of Anaesthesiology-Physical Status; BHT: Breath holding time.

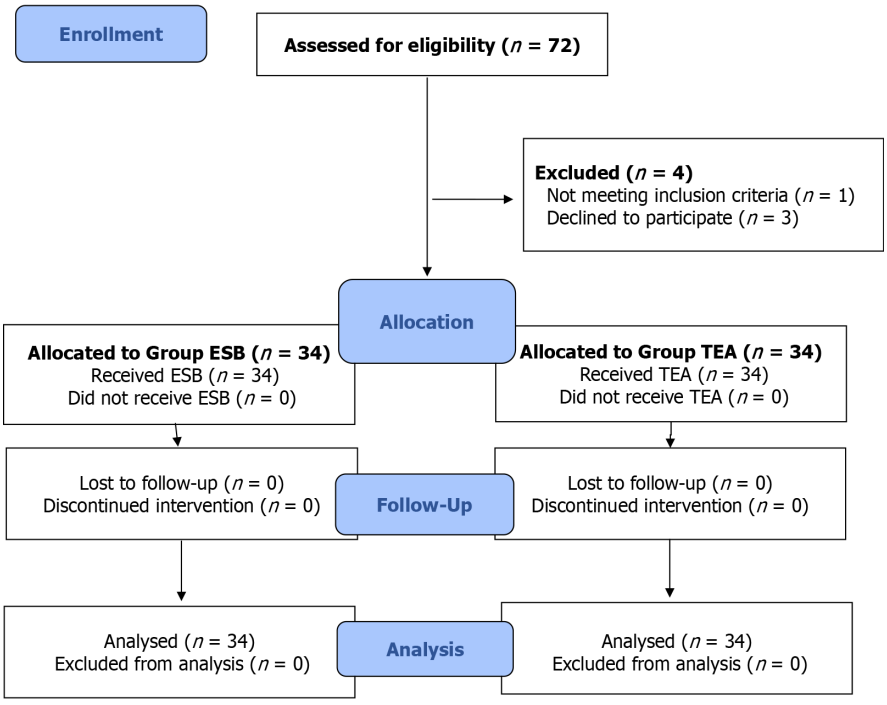


Figure 2 Strengthening the Reporting of Observational Studies in Epidemiology flow of participants. ESB: Erector spinae block; TEA: Thoracic epidural analgesia.

DISCUSSION

This study provides robust data on the comparative effectiveness of ESB and TEA in thoracotomy patients. However, its external validity is influenced by patient demographics, procedural expertise, resource availability, and institutional practices. TEA's superior analgesic efficacy and facilitation of pulmonary function recovery may render it the preferred technique in well-equipped centres. However, ESB offers a viable alternative in scenarios where hemodynamic stability is prioritized or where critical care resources are limited. Further studies in diverse populations and varied clinical settings are warranted to enhance the generalizability of these findings.

Table 2 Comparison of resting numerical rating scale, dynamic numerical rating scale, and number of balls lifted in spirometry after surgery between the two study groups, mean ± SD

Time post-extubation (hours)	ESB (*n* = 34)	TEA (*n* = 34)	*P* value
Resting NRS			
0	1.70 ± 1.03	1.05 ± 0.77	0.004[a]
6	1.64 ± 0.98	1.2 ± 0.88	0.055
12	2.17 ± 0.93	2.0 ± 1.10	0.480
24	2.76 ± 1.32	2.20 ± 1.32	0.080
36	2.64 ± 1.43	2.52 ± 1.18	0.710
48	3.29 ± 1.19	2.88 ± 1.25	0.170
72	3.2 ± 1.07	2.61 ± 0.92	0.010[a]
Dynamic NRS			
0	3.0 ± 1.3	1.7 ± 1.0	0.0001[a]
6	3.23 ± 1.23	1.9 ± 1.05	0.0001[a]
12	3.7 ± 1.08	2.8 ± 1.2	0.003[a]
24	4.29 ± 1.46	2.9 ± 1.4	0.0001[a]
36	4.23 ± 1.53	3.2 ± 1.2	0.0045[a]
48	4.64 ± 1.34	3.58 ± 1.30	0.0015[a]
72	4.52 ± 1.16	3.5 ± 0.99	0.0002[a]
Number of balls lifted in spirometry after surgery (1/2/3)			
0	10/22/2	2/25/7	0.015[a]
6	8/16/10	1/11/22	0.002[a]
12	10/10/14	1/7/26	0.003[a]
24	6/16/12	1/9/24	0.008[a]
36	4/18/12	1/12/21	0.060
48	4/18/12	1/9/24	0.020[a]
72	4/16/14	1/6/27	0.005[a]

[a]*P* indicates significant value.

ESB: Erector spinae plane block; TEA: Thoracic epidural anaesthesia; NRS: Numerical rating scale.

In thoracotomy patients, when regional analgesia is insufficient, opioids become the primary option for pain management. However, opioid use is associated with several side effects, including respiratory depression, nausea, vomiting, pruritus, delayed bowel function, and opioid dependence[4,5]. Thus, minimizing opioid consumption is crucial [18]. TEA, a well-established approach for thoracotomy pain, effectively reduces opioid requirements[4,5,17-19]. Forero *et al*[13,20] demonstrated that ESB is a simple and safe alternative for thoracic analgesia in both chronic neuropathic pain as well as acute postsurgical or post-traumatic pain. Hamilton *et al*[21] explained that by depositing local anaesthetic deep to the erector spinae muscle, *i.e.*, in close proximity to the costotransverse foramina, ESB blocks both the dorsal and ventral rami of the thoracic spinal nerves at origin, and a continuous catheter inserted in this plane relieves pain in patient with multiple unilateral rib fractures. Thus, ESB can reduce the need of opioids in management of thoracotomy pain.

Singh *et al*[18] compared unilateral USG-guided ESB with TEA in paediatric thoracotomy patients and found comparable postoperative opioid-sparing effect. Similarly, our study demonstrated no significant difference in rescue opioid requirements between the ESB and TEA groups following antero-lateral thoracotomy.

However, the time required for block execution differed between the two studies. Singh *et al*[18] reported a shorter block performance time for ESB compared to TEA, while in our study, the ESB group had a significantly longer block performance time. This discrepancy can be attributed to several factors. In our adult population, acquiring a satisfactory ultrasound image for ESB often required more time due to anatomical variability, increased tissue depth, and patient habitus. In contrast, epidural placement, being a more routine and familiar procedure, was generally quicker. In pediatric patients, as studied by Singh *et al*[18], the relatively superficial anatomy may facilitate ultrasound visualization, but the difficulty in reliably palpating landmarks and the need for additional care during positioning can prolong epidural placement.

Table 3 Comparison of mean arterial pressure and postoperative inotropic requirement between the two study groups

Time post-extubation (hours)	ESB (*n* = 34)	TEA (*n* = 34)	*P* value
MAP			
0	68.4 ± 3.15	58.8 ± 5.02	< 0.0001[a]
6	68.4 ± 6.16	60.2 ± 6.04	< 0.0001[a]
12	70.4 ± 5.58	61.2 ± 4.11	< 0.0001[a]
24	69.5 ± 5.08	63.14 ± 3.4	< 0.0001[a]
36	71.7 ± 4.8	64.7 ± 2.0	< 0.0001[a]
48	72.4 ± 4.36	64.58 ± 2.68	< 0.0001[a]
72	72.0 ± 4.36	65.8 ± 2.78	< 0.0001[a]
Proportion of patients with postoperative inotropic requirement			
0	0/34	14/34	0.001[a]
6	2/34	14/34	0.0012[a]
12	2/34	8/34	0.08
24	2/34	6/34	0.260
36	0/34	0/34	1.00
48	0/34	0/34	1.00
72	0/34	0/34	1.00

[a]*P* indicates significant value.
ESB: Erector spinae plane block; TEA: Thoracic epidural anaesthesia; MAP: Mean arterial pressure.

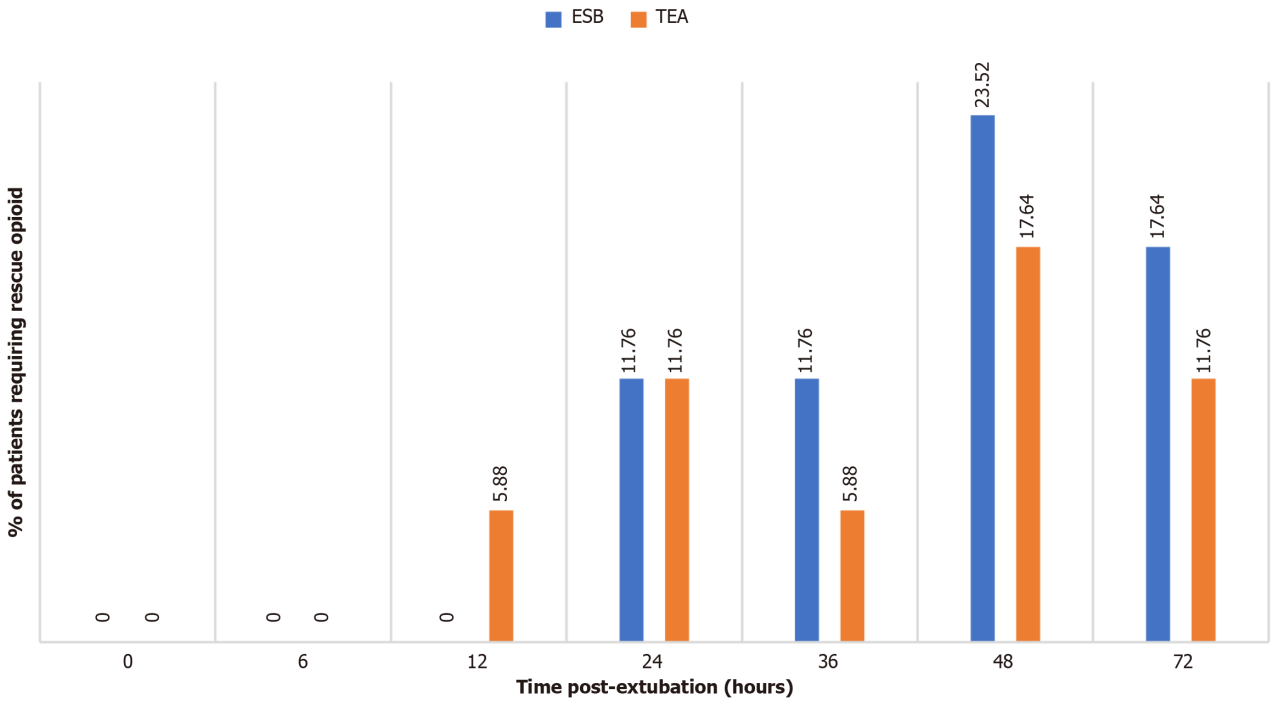


Figure 3 Proportion of patients requiring rescue opioid at various time-points post-extubation. ESB: Erector spinae block; TEA: Thoracic epidural analgesia.

In our study, the resting NRS scores were significantly higher in the ESB group at 0 hours, 6 hours, and 72 hours and were comparable between the two groups at all other time-points. The dynamic NRS scores were significantly higher in the ESB group at all time-points post-extubation. These results are consistent with the study done by van den Broek *et al* [22]. Similarly, Nagaraja *et al*[4] observed that TEA was more effective than ESB in cardiac surgery patients, particularly in reducing movement-associated pain. Also, Hong *et al*[23] conducted a study comparing ESB to TEA for postoperative pain in video-assisted thoracic surgery and demonstrated that patients in the ESB group reported more pain and experienced fewer complications, such as nausea, dizziness, and hypotension. However, Singh *et al*[18] reported comparable pain scores between ESB and TEA in pediatric thoracotomy patients, suggesting that ESB may be equally effective in specific populations. This discrepancy could be attributed to differences in surgical approach (open thoracotomy *vs* video-assisted thoracoscopic surgery), patient age, or local anesthetic dosing. Our study, focusing on adult antero-lateral thoracotomy, supports the notion that TEA remains superior for dynamic pain control, possibly due to its more extensive blockade of thoracic dermatomes.

In the present study, the postoperative respiratory efforts were assessed by the number of balls raised in the spirometer, which indicates the peak inspiratory flow rate. The proportion of patient lifting three balls was significantly higher in the TEA group, suggesting a better pain control and potentially a better lung recruitment in the TEA group. This aligns with Joshi *et al*[9] who emphasized that effective analgesia is critical for preventing postoperative pulmonary complications such as atelectasis.

Multiple studies have consistently shown that TEA is associated with a higher risk of hypotension compared to ESB[18,19,24]. This trend has been observed across various surgical contexts - including thoracic trauma, hepatic surgery, and pediatric thoracotomy - where TEA often results in significant hemodynamic disturbances, likely due to its more extensive sympathetic blockade[18,19,24]. In contrast, ESB by targeting the dorsal rami of spinal nerves and sparing significant autonomic fibers, tends to preserve hemodynamic stability. Our findings align with this pattern, as the TEA group in our study exhibited significantly lower MAPs and higher postoperative inotropic requirements compared to the ESB group. These results reinforce the emerging view that ESB may offer a safer hemodynamic profile, particularly in patients at risk of instability.

Given these findings, the choice between ESB and TEA should be individualized based on patient factors and institutional resources. TEA may be preferable in centers with advanced hemodynamic monitoring, particularly for patients undergoing extensive thoracic resections where dynamic pain control is paramount, while ESB offers a safer alternative in resource-limited settings or for patients at high risk of hypotension (*e.g.*, elderly, those with cardiac comorbidities).

This study has several limitations. First, patient allocation to ESB or TEA was based on anesthesiologist preference rather than randomization, introducing potential selection bias. Second, the lack of blinding for clinicians and patients may have influenced pain assessments and postoperative management. Third, the single-center design and limited sample size may restrict generalizability to other settings with differing patient demographics or surgical practices. Fourth, using a fixed local anesthetic infusion rate for all patients, without titration based on individual pain responses may have affected outcomes; a patient-controlled analgesia system or variable dosing could have optimized pain control. Finally, although all patients underwent antero-lateral thoracotomy, variations in surgical technique, tissue trauma, or surgeon experience may have confounded the comparison between ESB and TEA.

CONCLUSION

Both continuous unilateral ESB and TEA provide effective opioid-sparing postoperative analgesia for patients undergoing antero-lateral thoracotomy. While TEA demonstrates superior analgesic efficacy compared to ultrasound-guided unilateral ESB, it is associated with a higher incidence of postoperative hypotension and greater inotropic requirements.

FOOTNOTES

Author contributions: Jain A and Trivedi S designed the research study, and they contributed equally to this article as co-first authors; Jain A, Kaushal A, Kumar H, Karna ST, Ahmad Z, and Trivedi S performed the research, analyzed the data, and wrote the manuscript; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Prospective Study

Effectiveness, safety, and feasibility of outpatient parenteral antimicrobial therapy in a resource-limited setting: A pilot longitudinal study

Amit Kumar, Prasan Kumar Panda

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Abstract

BACKGROUND

Outpatient parenteral antimicrobial therapy (OPAT) offers a crucial method for administering intravenous/intramuscular antimicrobials outside of hospital settings, allowing patients to complete treatment safely while avoiding many hospital-acquired complications. This is a major boost or low-hanging fruit intervention in antimicrobial stewardship practices with multiple targets like decreasing hospital stays, its related complications, the economy, the burden on hospitals, *etc.* However, resource-constrained countries like India practices rarely OPAT in an evidence-based way.

AIM

To evaluate the effectiveness, safety, and feasibility along with barriers and facilitators of OPAT practices in resource-poor settings, with a focus on its role in antimicrobial stewardship.

METHODS

This pilot longitudinal observational study included patients who met OPAT checklist criteria and were committed to post-discharge follow-up. Pre-discharge education and counselling were provided, and demographic data were recorded. Various outcome measures, including barriers and facilitators, were identified through an extensive literature review, fishbone diagram preparation, data collection and analysis, and patient feedback. All healthcare workers who were taking care of the patients discharged with OPAT were contacted with open-ended questions to get data on feasibility. The study was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences, Rishikesh. We used descriptive analysis and the χ^2 test to analyze data. P value < 0.05 was considered significant.

RESULTS
Out of 20 patients, the mean age was 37 years. The cohort comprised 13 males. OPAT was administered at home in 15 cases and at nursing homes in 5 cases, with nine patients receiving treatment from family members and 11 patients receiving care from a local nurse. The infections requiring OPAT included: Kidney-urinary tract (6 cases), gastrointestinal tract (4 cases), respiratory tract (4 cases), meningitis (3 cases), endocarditis (2 cases), and multiple visceral abscesses (1 case). Nineteen out of 20 patients achieved afebrile status. Half of the patients did not receive education, counselling, or demonstrations prior to discharge, but all patients rated the service as good/excellent. According to doctors' feedback, OPAT is highly beneficial and effective for patients when systematically implemented with daily telephonic monitoring, but faces challenges due to the lack of standardized protocols, dedicated teams, and adequate resources. The implementation of OPAT resulted in a reduction of hospitalization duration by an average of two weeks.

CONCLUSION
This pilot study proves that OPAT is safe, feasible, and efficacious by reducing two weeks of hospitalization in resource-poor settings. OPAT contributes directly to antimicrobial stewardship by reducing hospital stays and hospital-acquired complications, which is vital in combating antimicrobial resistance (AMR) and aligns with the global action plan for AMR in infection prevention and optimal antimicrobial utilization.

Key Words: Antimicrobial resistance; Barriers and facilitators; Integrated antimicrobial stewardship; Outpatient parenteral antimicrobial therapy; Telephonic monitoring

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Core Tip: There is a lack of knowledge about the outpatient parenteral antimicrobial therapy (OPAT) practice among healthcare workers (HCWs), including those working in tertiary care settings. To improve the quality of OPAT practice, systematic implementation of standardized protocols, dedicated teams, and comprehensive pre-discharge education for patients and caregivers is essential. Enhancing these elements can further bolster antimicrobial stewardship and contribute to global efforts against antimicrobial resistance. This can be done by organizing training sessions for all HCWs involved in patient care.

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INTRODUCTION

Outpatient parenteral antimicrobial therapy (OPAT) has become essential in the continuum of care for patients requiring long-term antimicrobial therapy outside hospital settings. Its implementation is critical in reducing hospital admissions, lowering healthcare costs, and minimising the risks associated with prolonged hospital stays, such as nosocomial infections[1]. However, more extensive research is needed to fully understand the economic analysis of OPAT in resource-limited settings. OPAT programs have not been successfully implemented in low-income or middle-income countries except Japan[2], where they have been found to be a safe and feasible modality for treating certain types of infections. OPAT is now routinely employed for patients requiring intravenous antimicrobial therapy for a variety of infective conditions, including endocarditis, osteomyelitis, and prosthetic joint infection, enabling early hospital discharge. However, there is no exact epidemiological data on common infections requiring OPAT. For some conditions (such as cellulitis), initiation of OPAT in the outpatient or emergency department setting may allow avoidance of hospitalisation entirely[3,4]. As part of broader antimicrobial stewardship efforts, OPAT enables the rational use of antimicrobials, thus playing a significant role in combating antimicrobial resistance (AMR), a growing global health concern[5]. However, despite its benefits, the widespread adoption of OPAT faces several barriers, while various facilitators exist that can enhance its practice. Particularly, in resource-limited settings, specific challenges include limited healthcare infrastructure like lack of home infusion service and essential equipment to monitor vital signs. Additionally, there are inadequate laboratory facilities for monitoring biochemical, microbiological, and pathological parameters. These challenges are further compounded by the unavailability of necessary drugs and a shortage of trained healthcare workers (HCWs), particularly in rural areas, where infectious disease specialists are scarce and rarely available. One of the primary barriers to the effective implementation of OPAT is the lack of standardized guidelines and protocols, which leads to variability in practice. This inconsistency can result in suboptimal patient outcomes, such as treatment failures, adverse drug reactions or AMR[6]. Furthermore, the complexity of coordinating care among multiple healthcare providers, including infectious disease specialists, nurses, and pharmacists, often hampers the seamless delivery of OPAT

services[7]. Additionally, limited access to trained healthcare professionals and specialized equipment in outpatient settings can further impede the successful administration of OPAT[8].

Financial constraints also present significant challenges. The cost of antimicrobial agents, infusion equipment, and the need for frequent monitoring can be prohibitive, especially in low-resource settings[9]. Moreover, the reimbursement policies for OPAT services vary widely across regions, often discouraging healthcare providers from offering these services[10]. Patient-related factors, such as adherence challenges due to lacking transportation, forgetting appointments and storing medications out of the recommended range temperature, safety concerns, logistical issues related to home-based care, and the psychological burden of managing complex treatments at home, also contribute to the barriers[11].

On the other hand, facilitators that can enhance the practice of OPAT include the development of multidisciplinary teams and robust communication channels among healthcare providers[12]. Advances in telemedicine and remote monitoring technologies have also emerged as crucial facilitators, allowing for real-time patient monitoring and timely interventions, thus improving patient outcomes and satisfaction[13]. Furthermore, educational initiatives aimed at both healthcare providers and patients have been shown to enhance adherence to OPAT protocols and optimize antimicrobial use[14]. Addressing these barriers and leveraging the facilitators are crucial steps in integrating OPAT into broader antimicrobial stewardship strategies, ultimately helping to curb the rise of AMR.

In a resource-restrained environment, there is no standard guideline to practice OPAT, hence it is not routinely practised due to the absence of health insurance coverage, lack of trained personnel and limited outpatient infrastructure. In India, the burden of infections and AMR is significant, with 297000 deaths attributable to AMR and 1042500 deaths associated with AMR in 2019. Previous studies on OPAT in resource-limited settings have not assessed long-term outcomes or patient safety in a longitudinal format. Additionally, OPAT has not been extensively tested in this particular context due to concerns regarding safety and feasibility. A pilot longitudinal observational study was conducted to gather preliminary data on the operational challenges and to assess the effectiveness, safety, and feasibility of OPAT, as well as to identify the barriers and facilitators in a resource-limited tertiary care hospital setting. Conducting a larger-scale study could overlook critical factors impacting the program's success, without such data.

MATERIALS AND METHODS

Study design

We conducted a pilot longitudinal observational study with above objectives at All India Institute of Medical Sciences (AIIMS), Rishikesh, India (a resource poor setting) between December 2023 and May 2024.

Study population

We recruited 20 patients who were administered OPAT from the Department of General Medicine, AIIMS Rishikesh. A predefined OPAT checklist was utilized to evaluate each patient's eligibility for OPAT. Only those patients who met the criteria outlined in the OPAT checklist and demonstrated a willingness to adhere to a structured follow-up regimen post-discharge were discharged with OPAT recommendations. A total of 20 patients met these criteria and were included in the study. This method ensured that the study cohort consisted solely of patients deemed capable of effectively participating in the OPAT regimen.

The OPAT checklist used for patient selection was: (1) Patient does not require hospitalization for any intervention; (2) Patient is vitally stable or clinically improved to a state of discharge; (3) Patient is capable of safe and effective IV/IM drug administration at home; (4) Therapeutic monitoring is feasible over a phone/outpatient department (OPD) basis; (5) Drug storage is feasible in patient's home; and (6) Patient is willing to start and participate in a sharing decision resulting in a signed (patient and doctor) page of this.

The study utilized various antimicrobial agents, with the selection of specific agents being determined by the type of infection and individual patient factors. Pre-discharge education and counselling were provided, and demographic details, including patient contact information, were recorded before discharge. Patients were advised to attend follow-up appointments at the OPD as directed by the treating physician and to maintain telephonic communication.

Daily monitoring of patients discharged with OPAT was conducted telephonically by the treating physician to assess effectiveness, safety, and feasibility. This monitoring included the following: (1) The primary setting where OPAT was administered (*e.g.*, home, outpatient clinic, infusion centre, skilled nursing facility, or physician's office); (2) The individual responsible for administering OPAT (*e.g.*, family members, local nurse, or physician); (3) Assessment of clinical improvements, specifically the resolution of primary symptoms; (4) Identification of any new symptoms; (5) Monitoring for adverse events related to the medication or vascular access, including adherence to the prescribed regimen, cannula changes every third day, or immediate replacement if complications such as swelling, redness at the cannula site, or fever with chills and rigor occurred; (6) Documentation of any premature cessation of OPAT administration and the reasons for such discontinuation; and (7) Close daily follow-up ensured that any complications or deviations from the treatment protocol were promptly addressed. Additionally, feedbacks from patients and HCWs were collected following the completion of the treatment course.

While practising the OPAT, many barriers and facilitators were observed and identified in the fishbone diagram, prepared after an extensive literature review and feedback from patients and HCWs (they were contacted with open-ended questions to get data on feasibility). Additional details, including the type of infection, the antimicrobial agent prescribed, and the corresponding dosage and duration, were obtained from patient records by accessing the Medical Records Department of the hospital.

Statistics analysis

We used descriptive analysis and the χ^2 to analyze data. *P* value < 0.05 was considered significant. Descriptive statistics were employed to summarize patient demographics, clinical outcomes and gender distribution. Frequencies and percentages were used to categorize infections and antimicrobial agents administered. Patient outcomes were quantified and clinical improvement was tracked through follow-up data. Statistical comparisons were made regarding treatment duration. Barriers and facilitators identified through patient feedback were analyzed.

Ethical consideration

The approval to conduct this research was taken from the Institutional Ethics Committee of AIIMS, Rishikesh, India. To maintain privacy, any data that may have identified the individual participants of the study was not disclosed.

RESULTS

The majority of patients were middle-aged, with males constituting over 50% of the cohort (Table 1). OPAT was primarily administered in the home setting, and in more than half of the cases, local health nurses facilitated the treatment.

Table 1 Basic characteristics of the cohort studied (*n* = 20)

Parameters	Value
Mean age	37 years (age range = 21-63 year)
Gender distribution	
Male	13
Female	7
Site of OPAT administration	
Home	15
Nursing home	5
Administration method	
Administered by family members	9
Administered by local nurse	11

OPAT: Outpatient parenteral antimicrobial therapy.

The majority of infections requiring OPAT were from kidney-urinary, gastrointestinal tract, or respiratory tracts (Figure 1A). All the patients achieved afebrile status. Two patients, with diagnosis of enteric fever, discontinued their OPAT regimens prematurely one after 6 days and the other after 8 days. Both patients demonstrated clinical improvement, with no fever spikes, and reported complete resolution of symptoms, including improved appetite and sleep. They remained afebrile throughout a 3-month follow-up period. One patient was readmitted due to the inability to administer OPAT at home because of the unavailability of the medication and a caregiver. This patient experienced fever for 4-5 days before receiving assistance from a local nurse. The patient subsequently became afebrile after 5-days. After 3-months of follow-up, he showed complete resolution of infection as confirmed by radiological and microbiological evaluations. Additionally, one patient developed thrombophlebitis. It was noted that approximately half of the patients did not receive education, counselling, or demonstrations before discharge. However, all patients rated the service as good/excellent and stated that they would choose the OPAT service again. The implementation of OPAT resulted in a reduction of hospitalization duration by an average of two weeks, thereby lowering hospitalization costs without compromising clinical efficacy.

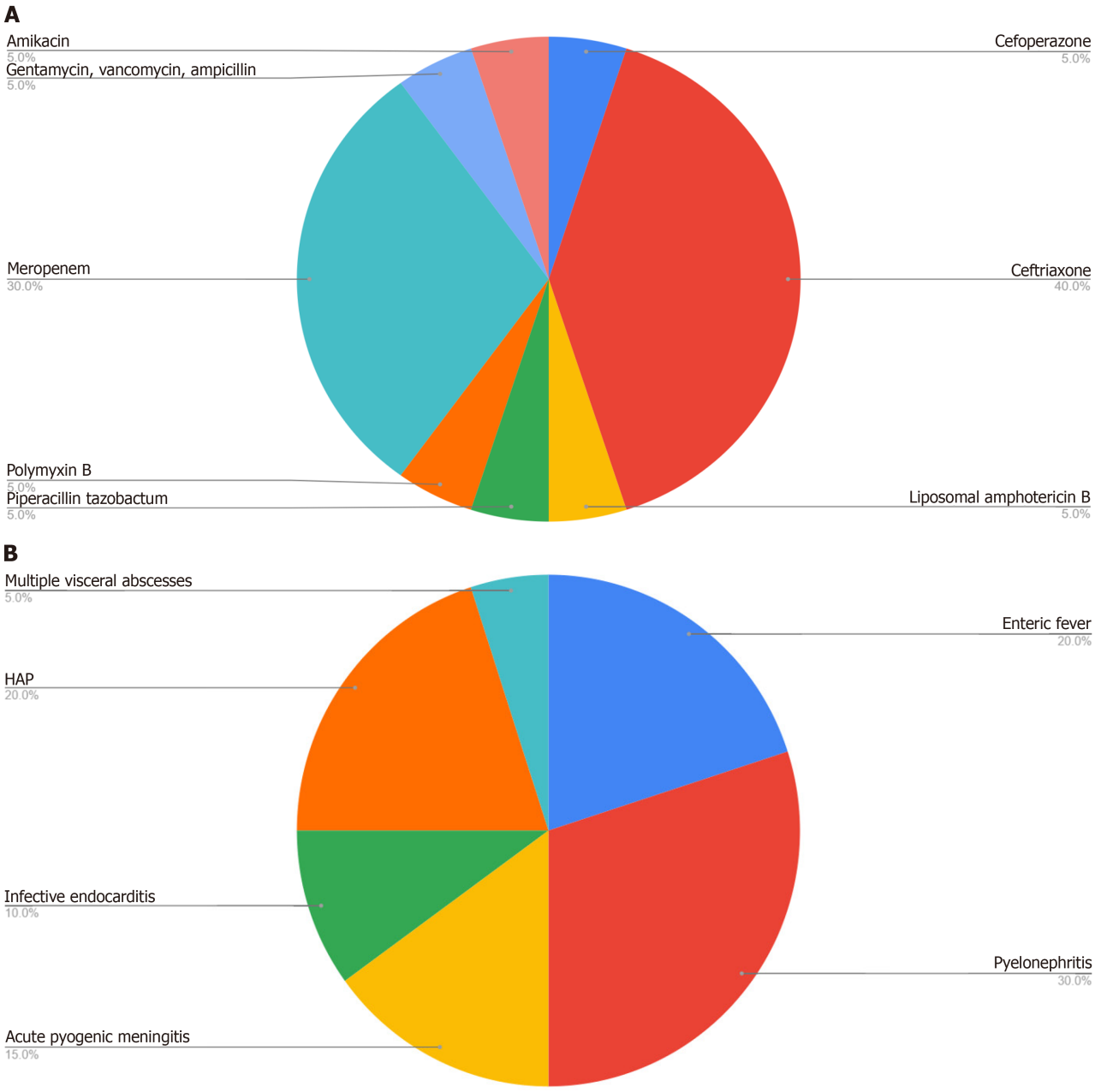


Figure 1 Pie chart representing the distribution of antimicrobials and infections among the 20 patients in the study. A: Distribution of antimicrobials; B: Distribution of infections.

Ceftriaxone was the most frequently prescribed antimicrobial, used in 8 of the 20 cases (Figure 1B). The average duration of OPAT was 14 days, with a range extending from 5 days to 6 weeks, the latter being for cases of fungal pyelonephritis.

Various barriers and facilitators were identified and represented in a fishbone diagram (Figure 2). Barriers to OPAT implementation included inadequate training of HCWs and communication gaps among them. The lack of standardized procedures also hampered effective OPAT processes. Equipment-related challenges involved non availability of equipment, lack of knowledge of their functioning and maintenance and insufficient storage for antimicrobials, while the home environment often lacked suitability for proper administration and care, including absence of caregiver, remote location and no accessibility to nearby OPAT centers. Facilitators included training programs for HCWs emphasizing on daily telephonic monitoring ensuring OPAT compliance and early identification of any complication and its management, advanced infusion devices with safety features, standardized protocols, and caregiver education to ensure proper support and hygiene.

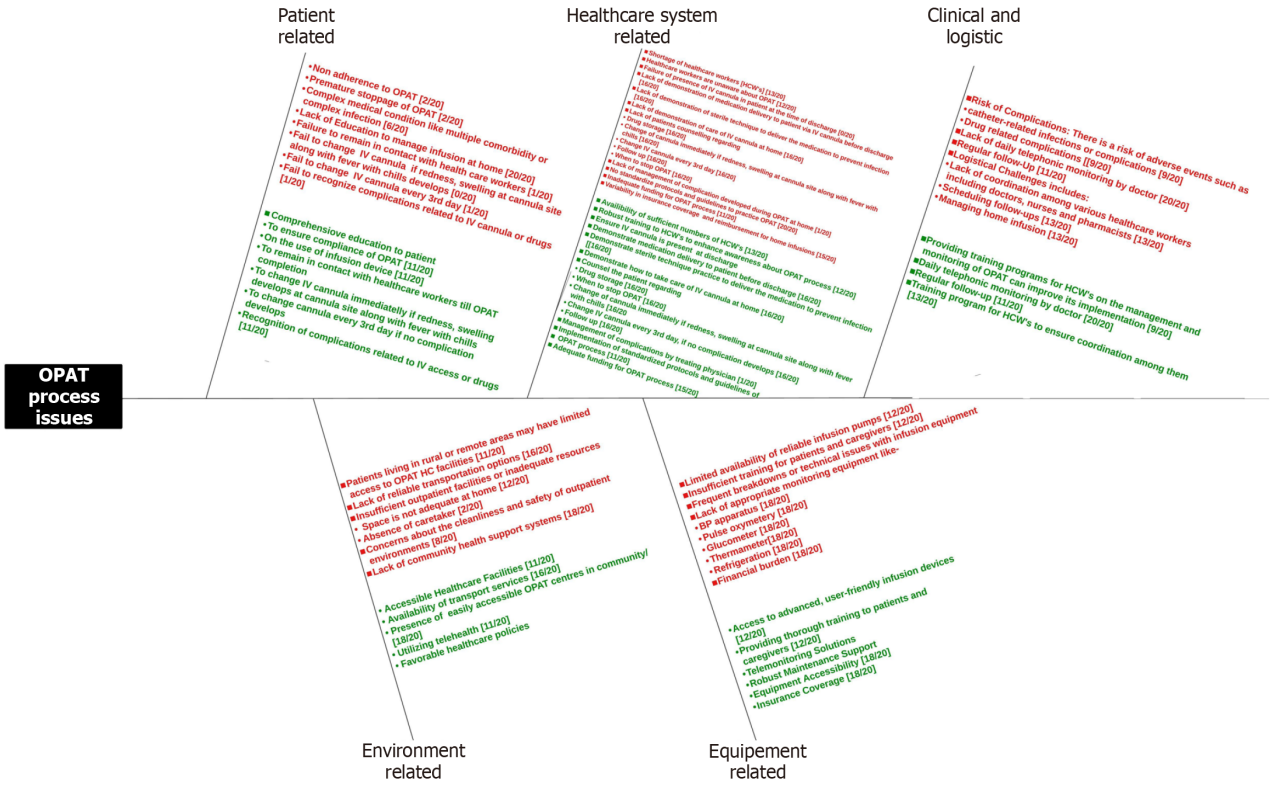


Figure 2 Various barriers and facilitators identified and represented in a fishbone diagram in the study. OPAT: Outpatient parenteral antimicrobial therapy.

DISCUSSION

OPAT represents a significant advancement in healthcare delivery, particularly in resource-poor settings where hospital resources are limited and the burden of infectious diseases is high. Despite its potential to enhance patient care and reduce healthcare costs, the implementation of OPAT faces several challenges that need to be addressed to maximize its effectiveness. This discussion explores the key issues and considerations surrounding OPAT practice in such settings, focusing on patient adherence, healthcare infrastructure, financial implications, and its role in antimicrobial stewardship.

The findings of this pilot study offer significant insights into the role of OPAT as a 100% effective alternative for managing a variety of infections and its potential impact on healthcare resource utilisation. The study demonstrates that OPAT is a viable approach for treating a broad spectrum of infections, including complicated urinary tract infections, enteric fever, hospital-acquired pneumonia, acute pyogenic meningitis, infective endocarditis, and multiple visceral abscesses. In this study, a majority of patients (95%) exhibited clinical improvement and resolution of infections within two weeks, with a single case requiring one and a half months of follow-up for resolution. These results underscore the efficacy of OPAT in administering IV antimicrobials outside of acute care hospital settings. Hitchcock *et al*[15] report on a case series of 303 episodes of OPAT care, in a resource-rich setting. found readmission in 23 episodes (7.6%), and two patients lost vascular access, resulting in the early termination of OPAT. Of the remaining 273 episodes of care, over 95% of cases were resolved with a single course of antibiotics and few adverse events were reported. A series of 334 episodes of OPAT care was reported by Chapman *et al*[16]. A total of 87% of patients across all diagnoses were classified as improved or cured (92% when including skin and soft tissue infections only). Twenty-one patients (6.3%) were readmitted, although 12 of these were for reasons unrelated to OPAT. The group also looked to address the issue of patient satisfaction. Of 449 patients surveyed, 276 responded (61%). 272 (98.6%) rated the service as very good or excellent, and 275 (99.6%) stated that they would choose the OPAT service again[16]. In our study, there was 1 readmission (5%), 1 patient developed thrombophlebitis (5%) and 100% cases resolved after OPAT therapy. In resource-poor settings, a study in Japan similar to our study highlights a high cure rate and low readmission rate, which reflect careful patient selection, reduced hospitalization duration and saved bed days[2].

The safety profile of OPAT in this case series was favorable. A comprehensive monitoring and adverse event reporting system facilitated the prompt detection and management of complications, such as thrombophlebitis, which was effectively managed with topical Thrombophob ointment. Some of the unexpected findings emerging from this study include 100% safety and effective treatment, low readmission rate (one patient) and relatively low adverse event (one case of thrombophlebitis). The likely reason for this favorable outcome is robust daily monitoring by the treating physician, and almost all patients came for follow-up. This outcome aligns with the growing body of evidence supporting OPAT's safety, thereby providing reassurance to both healthcare providers and patients in resource-poor settings.

Adherence is critical for the success of OPAT, as incomplete or incorrect administration of antimicrobials can lead to treatment failure, relapse, or the development of AMR[17]. Factors influencing adherence include the complexity of the treatment regimen, the patient's understanding of the therapy, and the support available from healthcare providers. In resource-poor settings, where access to healthcare professionals may be limited, ensuring adherence can be particularly challenging. Studies have shown that providing comprehensive education and counselling before discharge significantly improves adherence rates[18,19]. However, the pilot study indicates that nearly half of the patients did not receive adequate pre-discharge education, highlighting a critical gap in OPAT implementation that must be addressed to improve outcomes[20]. Beyond the lack of education, other patient related barriers affecting the OPAT adherence includes transportation difficulties, affordability of antibiotics and home hygiene challenges.

Healthcare infrastructure also plays a vital role in the successful implementation of OPAT. The availability of trained healthcare providers, such as nurses and pharmacists, who can administer and monitor therapy is essential. In many resource-poor settings, there is a shortage of such professionals, which limits the ability to deliver OPAT effectively[21]. Additionally, the lack of essential equipment, such as infusion pumps and telemedicine tools for remote monitoring, further complicates the delivery of OPAT. Innovative solutions, such as task-shifting and training community health workers to assist in OPAT, have shown promise in overcoming these barriers[22]. However, such interventions require careful planning and support from healthcare systems to be sustainable.

Financial considerations are another critical factor in OPAT practice. The cost of antimicrobials, particularly newer agents that are often required for resistant infections, can be prohibitive in resource-poor settings[23]. Furthermore, the costs associated with administering OPAT, including the need for frequent follow-up and monitoring, add to the financial burden on both healthcare systems and patients. In resource-poor setting, where healthcare resources are already limited, this financial burden may limit the patient's access to the necessary treatment and can result in OPAT failure. The variability in reimbursement policies exacerbates these challenges. Ensuring that OPAT is financially accessible requires policy interventions that address these cost barriers, potentially through subsidies, insurance coverage, or other forms of financial assistance[24]. Furthermore, the involvement of public-private partnerships in enhancing the affordability of OPAT services could also play a crucial role in addressing these financial challenges associated with OPAT. Despite challenges in resource-poor settings, the long-term feasibility of OPAT can be enhanced through comprehensive pre-discharge education, daily monitoring, telemedicine, effective management of complications, and adequate financial and infrastructure support.

OPAT's role in antimicrobial stewardship cannot be overstated. Since it was a pilot study, AMR monitoring was not done and it must be incorporated in future OPAT programs. In most cases, microbiological confirmation was not done, which is also crucial for antibiotic use optimization. By enabling the use of appropriate antimicrobials outside of hospital settings, OPAT reduces the risk of hospital-acquired infections and the subsequent need for broad-spectrum antibiotics, which are often overused in inpatient settings[25]. Furthermore, OPAT allows for the continuation of therapy with narrow-spectrum agents, aligning with the principles of antimicrobial stewardship by minimizing the selection pressure for resistant organisms[26]. The integration of OPAT into broader antimicrobial stewardship programs can help in optimizing antimicrobial use, reducing AMR rates, and ultimately improving patient outcomes. However, to achieve these benefits, OPAT programs must be carefully managed and supported by robust stewardship frameworks that include monitoring and feedback mechanisms[27]. At present, in India, OPAT is no where, but similar to any low-hanging fruits of stewardship practices such as 'color-coded charts for antimicrobial prescriptions' in a private hospital, this pilot project will go a long way[28].

OPAT can scale with the introduction of a reimbursement policy for all patients, provision of standard guidelines, training of HCWs, availability of ID physician improvements in infrastructure and patient access to medications. Governments should invest in training of HCWs, infrastructure building, medication access, and telemedicine for OPAT implementation. Furthermore, developing national guidelines will standardize OPAT care and address resource-limited setting challenges.

Limitations

It's important to acknowledge the limitations of this study, including the relatively small sample size, selection bias, and the single-center nature of the study. Further research with a larger sample size and multi-centre studies is needed to validate these findings and explore the broader applicability of OPAT in different healthcare settings. As this is a pilot study, the potential for selection bias was minimised by systematically screening all patients receiving intravenous antimicrobials for OPAT eligibility using a prespecified checklist. Additionally, to make the OPAT more successful and adverse event-free, a dedicated and well-trained team of HCWs is needed as well proper funding should be provided.

CONCLUSION

The results of this pilot study substantiate the 100% efficacy of OPAT in the management of diverse infections, while concurrently reducing hospitalization duration and associated costs. With a 95% rate of clinical improvement and a 100% safety profile, OPAT presents a robust alternative to traditional inpatient care, particularly in resource-constrained environments like India. Nonetheless, the study highlights significant challenges, including patient adherence, deficiencies in healthcare infrastructure, and financial constraints. Notably, nearly 50% of patients received inadequate pre-discharge education, which may hinder treatment success and contribute to the development of AMR. Structured OPAT programs with dedicated teams, task-shifting models, long-term research on cost-effectiveness, AMR reduction, and patient outcomes are essential to make this model more successful and accessible in future.

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FOOTNOTES

Author contributions: Kumar A contributed to the data collection and data analysis and was involved in manuscript writing; Panda PK provided the concept, interpreted the analysis, critically reviewed the draft, and approved it for publication along with Kumar A.

Institutional review board statement: The study was reviewed and approved by Institutional Ethics Committee, AIIMS Rishikesh, ensuring patient confidentiality, data protection, and adherence to ethical standards in research involving human participants.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We declare that we have no conflicts of interest.

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ORIGINAL ARTICLE

Basic Study

Preventive and therapeutic effects of magnesium sulfate on nikethamide-induced seizures: Implications for COVID-19 treatment

Dao-Jian Xu, Qiang Zhong, Guo-Tao Wang, Xiang Lu

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Peer-review model: Single blind

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Abstract

BACKGROUND

Nikethamide, a respiratory stimulant, is used to treat hypoxemia caused by coronavirus disease 2019 (COVID-19), but it carries a risk of convulsions. Magnesium sulfate ($MgSO_4$), a seizure inhibitor, might serve as a rescue agent against nikethamide-induced seizures.

AIM

To investigate the therapeutic effect of $MgSO_4$ on nikethamide -induced seizures in COVID-19 patients through animal experiments, providing experimental support for the clinical application of $MgSO_4$ in preventing and treating seizures caused by nikethamide.

METHODS

Forty mice were randomly divided into four groups: (1) Physiological saline; (2) Low-dose $MgSO_4$ (50 mg/kg); (3) Medium-dose $MgSO_4$ (100 mg/kg); and (4) High-dose $MgSO_4$ (200 mg/kg). After 15 minutes of intraperitoneal injection of different doses of $MgSO_4$ or an equal volume of physiological saline, the mice were injected with nikethamide (250 mg/kg).

RESULTS

Compared to the normal saline group, all doses of $MgSO_4$ significantly prolonged the seizure latency and reduced the severity of convulsions. However, they also extended the duration of seizures and correspondingly increased survival time ($P < 0.05$). The incidence of seizures and mortality rate in the $MgSO_4$-treated groups were significantly lower than those in the normal saline group ($P < 0.05$).

CONCLUSION

$MgSO_4$ can prevent and treat seizures caused by nikethamide in mice. This finding has implications for the application of $MgSO_4$ in treating and preventing seizures caused by nikethamide in COVID-19 treatment.

Key Words: COVID-19; Drug discovery; Hypoxemia; Magnesium sulfate; Nikethamide; Seizures

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Core Tip: Nikethamide is a respiratory stimulant used for the treatment of coronavirus disease 2019 (COVID-19); however, its use carries the risk of seizure induction. This study demonstrates that magnesium sulfate ($MgSO_4$) can effectively prevent and mitigate nikethamide-induced seizures in a dose-dependent manner. The results indicate that $MgSO_4$ prolongs seizure latency, reduces seizure severity, extends seizure duration, and decreases mortality in the experimental model. These findings provide important insights into the potential clinical application of $MgSO_4$ for managing nikethamide-associated seizure complications in COVID-19 patients.

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INTRODUCTION

Nikethamide is a respiratory stimulant that primarily acts by stimulating the respiratory center in the brainstem[1,2]. It has historically been used to treat central respiratory and circulatory failure, as well as to counteract central nervous system (CNS) depression caused by sedatives. However, at high doses, nikethamide is known to cause serious side effects, including vomiting, convulsions, and seizure-like symptoms[3]. These convulsive effects are primarily attributed to its ability to induce the prolonged abnormal opening of sodium ions (Na^+) channels, leading to excessive neuronal excitation[3,4].

In the context of coronavirus disease 2019 (COVID-19), nikethamide has been explored as a potential treatment for hypoxemia, particularly in critically ill patients[1]. Some studies suggest that nikethamide may improve oxygen saturation, enhance respiratory function, and reduce mortality[5]. However, there remains significant controversy regarding its efficacy in COVID-19 treatment, with conflicting reports on its clinical benefits[6]. Additionally, its use is limited due to the high risk of seizures, making it essential to identify effective strategies for preventing these adverse effects[7,8].

Magnesium sulfate ($MgSO_4$) is a well-established anticonvulsant widely used in conditions such as eclampsia[9]. It exerts its effects by inhibiting N-methyl-D-aspartate receptors (NMDARs) in a voltage-dependent manner[10,11]. Since excessive NMDAR activation is linked to seizure activity, $MgSO_4$ may serve as a potential rescue agent for nikethamide-induced seizures[12-14]. In addition to its anticonvulsant properties, $MgSO_4$ has been suggested to have potential benefits in COVID-19 treatment, including reducing hypoxia and inflammation[15]. However, its role in managing hypoxemia remains unclear, with inconsistent findings in clinical studies[16-18].

This study aimed to evaluate the preventive and therapeutic effects of $MgSO_4$ on nikethamide-induced seizures using an animal model. Specifically, we investigated whether $MgSO_4$ could prolong seizure latency, reduce convulsion severity, extend seizure duration, and improve the survival rate of mice treated with nikethamide. By elucidating its neuroprotective effects, the findings of this study may provide valuable insights for the clinical application of $MgSO_4$ in managing nikethamide-associated seizure complications in COVID-19 patients.

MATERIALS AND METHODS

Ethics approval

This study was conducted following the ethical guidelines for animal research and was approved by the Ethics Committee of Taizhou University.

Experimental animals

Forty pathogen-free Kunming mice, both male and female, weighing between 16 g and 18 g, were obtained from Zhejiang Weitong Lihua Laboratory Animal Technology Co., Ltd. (located in Jiaxing City, Zhejiang Province, China). The company holds the license number SYXK (Zhejiang Province) 2021-0013 and the production license number SCXK (Zhejiang Province) 2019-0001. Three days prior to the experiment, the mice were allowed to acclimate to the laboratory environment and had free access to food and water. To prevent potential behavioral differences among the mice from influencing the research results, all the experiments were conducted at the same time each day.

Drugs

The reagents utilized in this study included $MgSO_4$ produced by Tianjin Jinyao Pharmaceutical Co., Ltd. (Tianjin, China), with a batch number of H12020994 and a specification of 10 mL/2.5 g. Additionally, the experiment utilized nikethamide injection manufactured by Shanghai Hyundai Hasen Pharmaceutical Co., Ltd. (Shangqiu City, Henan Province, China), with a batch number of H20053727 and a specification of 1.5 mL/0.375 g. Furthermore, sodium chloride injection was provided by Shanghai Baxter Medical Products Co., Ltd. (Shanghai, China), with a batch number of H19983149 and a specification of 1000 mL/9 g.

Grouping and processing

Using a random number table, the mice were evenly and randomly allocated to four groups, namely, the saline control, low-dose $MgSO_4$ (50 mg/kg), medium-dose $MgSO_4$ (100 mg/kg), and high-dose $MgSO_4$ (200 mg/kg) groups, with 10 mice in each group. The mice were administered different doses of $MgSO_4$ or an equal volume of normal saline *via* intraperitoneal injection. After 15 minutes, each group of mice received an injection of nikethamide solution (250 mg/kg).

Observation indicators

The incubation period of convulsions (in seconds), duration of convulsions (in minutes), number of convulsions, and number of deaths among the mice in each group were observed and recorded. Compared to those prior to administration, convulsions were judged based on increased activity, such as walking, jumping, and irritability. The time from nikethamide injection to the appearance of convulsions was considered the incubation period of convulsions. The duration of convulsions was measured from the onset of convulsions to a state of silence in the mice. The time until death was calculated from the start of nikethamide injection to the moment of death.

Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences 26.0 (IBM Corp., Armonk, NY, United States), Excel 2019 (Microsoft Corporation, Redmond, WA, United States), and GraphPad Prism 8 (GraphPad Prism v8.0; GraphPad Software). The convulsion latency, convulsion duration, and time until death is expressed as the mean ± SD. Continuous quantitative data were compared among multiple groups using one-way analysis of variance (ANOVA), and Dunnett's *t* test was used for post hoc testing. Convulsion rates and mortality were expressed as percentages, and differences were compared using the rank sum test. A P value < 0.05 indicated a statistically significant difference.

RESULTS

Seizure latency

$MgSO_4$ significantly prolonged the incubation period to seizure onset in a dose-dependent manner. The control group exhibited a shortest latency of 80.30 seconds ± 22.32 seconds, whereas magnesium-treated groups showed progressively longer mean latencies: (1) 192.70 seconds ± 73.57 seconds at low dose; (2) 380.20 seconds ± 63.40 seconds at mid dose; and (3) 1129.50 seconds ± 252.51 seconds at high dose. Medium-dose and high-dose $MgSO_4$ groups had a significantly delayed seizure onset compared to control (P < 0.01 for each). Notably, the high-dose $MgSO_4$ group's latency was about 17 minutes longer than control (P < 0.001), with a mean difference of 1049.2 seconds (95%CI: 900.35–1198.05). An overall one-way ANOVA confirmed a significant effect of treatment on seizure latency (F-statistic = 121.12, P < 0.001). These findings demonstrate a clear dose–response relationship, as higher $MgSO_4$ doses yielded greater delays in seizure initiation, indicating that $MgSO_4$ effectively prolongs seizure onset in this model (Figure 1 and Table 1).

Seizure duration

In contrast to its effect on latency, $MgSO_4$ treatment led to longer seizure durations compared to control animals. The mean duration of seizure activity in the control group was 25.80 minutes ± 3.58 minutes, whereas animals receiving $MgSO_4$ experienced extended seizure episodes (low dose: 81.10 minutes ± 6.33 minutes; mid dose: 70.20 minutes ± 18.03 minutes; high dose: 75.20 minutes ± 10.68 minutes). All magnesium-treated groups had significantly increased seizure durations relative to control. Specifically, the high-dose group had a seizure duration approximately 3 times longer than control (P < 0.01), and even the low-dose group showed a notable increase (P < 0.01 *vs* control). Statistical analysis (ANOVA with post hoc comparisons) confirmed these differences, with P values < 0.01 for each group (*vs* control). This result suggests that while $MgSO_4$ delays the onset of seizures, once seizures begin, they persist longer in treated animals. One explanation is that magnesium's protective effects prevent early mortality or catastrophic seizure termination, thereby allowing seizures to continue for a prolonged period compared to the untreated controls (Figure 1 and Table 1).

Survival time

$MgSO_4$ markedly improved survival time following seizure induction, with higher doses conferring greater benefit. Control animals succumbed quickly, with a mean survival time of only 30.10 minutes ± 5.90 minutes post-seizure onset. In contrast, $MgSO_4$-treated groups survived substantially longer on average: (1) 83.10 minutes ± 5.53 minutes for the low-dose group; (2) 86.50 minutes ± 19.60 minutes for the mid-dose group; and (3) 111.70 minutes ± 17.23 minutes for the high-dose group. Collectively, the data indicate that $MgSO_4$ treatment improved overall survival in a dose-validated manner. The extended survival times in $MgSO_4$ groups highlight its neuroprotective role, as treated animals were able to

Table 1 Comparison of incubation period, duration and time until death of mice in each group

Groups (n = 10)	Variable group	Time (mean ± SD)	95%CI	P value
Normal saline control group	1	80.30 ± 22.32	64.33-96.27	-
Low-dose $MgSO_4$ group	1	192.70 ± 73.57	140.07-245.33	0.174
Medium-dose $MgSO_4$ group	1	380.20 ± 63.40[b]	334.85-425.55	< 0.01
High-dose $MgSO_4$ group	1	1129.50 ± 252.51[b]	948.86-1310.14	< 0.01
Normal saline control group	2	25.80 ± 3.58	23.24-28.36	-
Low-dose $MgSO_4$ group	2	81.10 ± 6.33[b]	76.57-85.63	< 0.01
Medium-dose $MgSO_4$ group	2	70.20 ± 18.03[b]	57.30-83.10	< 0.01
High-dose $MgSO_4$ group	2	75.20 ± 10.68[b]	67.56-82.84	< 0.01
Normal saline control group	3	30.10 ± 5.90	25.88-34.32	-
Low-dose $MgSO_4$ group	3	83.10 ± 5.53[b]	79.15-87.05	< 0.01
Medium-dose $MgSO_4$ group	3	86.50 ± 19.60[b]	72.48-100.52	< 0.01
High-dose $MgSO_4$ group	3	111.70 ± 17.23[b]	99.37-124.03	< 0.01

[b]P < 0.01, statistical differences are highly significant.
1: Incubation period (second); 2: Duration time (minute); 3: Survival time (minute). $MgSO_4$: Magnesium sulfate.

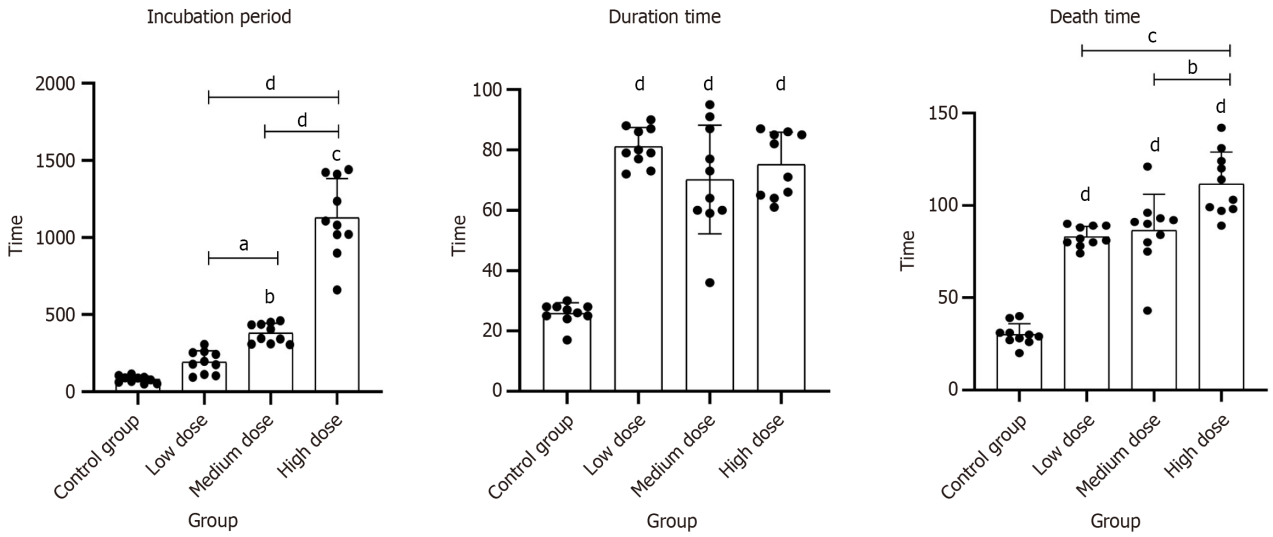


Figure 1 Comparison of incubation period, duration time, and death time among different groups. The figure presents the comparison of three variables—incubation period, duration time, and death time—among the control, low dose, medium dose, and high dose groups. Each dot represents an individual data point, and the error bars indicate the standard deviation. Statistical significance is marked with asterisks: (1) [a]P < 0.05; (2) [b]P < 0.01; (3) [c]P < 0.001; and (4) [d]P < 0.0001. Horizontal lines with asterisks above bars denote significant differences between the two connected groups, while asterisks directly above bars indicate significant differences compared to the control group.

withstand seizure activity longer without succumbing. This suggests that higher doses of $MgSO_4$ confer significant protection against lethal seizure consequences, underlining its potential therapeutic value in mitigating seizure-induced mortality (Figure 1 and Table 1).

Convulsion rate and mortality analysis

$MgSO_4$ exhibited a dose-dependent protective effect by reducing both convulsion incidence and mortality rates (Table 2). The low-dose group showed a convulsion rate of 90% and a mortality rate of 70%, with no significant difference from the control group (P > 0.99). The medium-dose group exhibited a moderate reduction in convulsion rate (60%) and mortality rate (30%), though the differences remained statistically non-significant (P > 0.05). In contrast, the high-dose group demonstrated a significant decrease in both convulsion incidence (20%, P = 0.045) and mortality (10%, P < 0.01), indicating a substantial neuroprotective effect. These results suggest that higher doses of $MgSO_4$ effectively mitigate seizure severity and significantly improve survival outcomes, whereas lower doses may be insufficient to confer full protection. The findings highlight the importance of dose optimization in clinical applications, reinforcing the potential of

Table 2 Comparison of convulsion rate and mortality of mice in each group

Group	Convulsion rate (%)	*H* value	*P* value	Mortality rate (%)	*H* value	*P* value
Low-dose $MgSO_4$ group	90	0.00	> 0.99	70	0.471	> 0.99
Medium-dose $MgSO_4$ group	60	0.668	> 0.99	30	5.051	0.356
High-dose $MgSO_4$ group	20	2.670	0.045[a]	10	9.899	< 0.01[b]

[a]$P < 0.05$, differences are statistically significant.

[b]$P < 0.01$, statistical differences are highly significant.

Control group: The control group in this study was the saline control group, in which mice received an equal volume of saline solution without magnesium sulfate. $MgSO_4$: Magnesium sulfate.

$MgSO_4$ as a therapeutic strategy for managing pharmacologically induced seizures.

DISCUSSION

In this study, we demonstrated that $MgSO_4$ significantly protects against nikethamide-induced seizures in mice. All doses of $MgSO_4$ prolonged the seizure latency and increased post-seizure survival time compared to saline, with medium (100 mg/kg) and high (200 mg/kg) doses producing especially strong effects. These doses also significantly reduced the intensity of convulsions and prolonged the duration of seizures. Compared with the control group, the incidence of seizures and mortality rate were significantly lower in the high-dose group. Notably, the anticonvulsant efficacy of $MgSO_4$ was dose-dependent. However, animals receiving the high dose exhibited signs of CNS depression (lethargy and even brief loss of consciousness in some cases), indicating that while seizures were well-controlled, excessive sedation occurred at the highest dose. Only one mouse in the high-dose group succumbed during the experiment, suggesting that 200 mg/kg, though sedating, did not reach a lethal threshold in this model. In summary, $MgSO_4$ dose-dependently prevented or mitigated the convulsive effects of nikethamide—prolonging the seizure-free interval, reducing seizure severity, extending seizure duration, improving survival, and lowering seizure frequency and mortality—albeit with observable sedation at high doses. These findings confirm our hypothesis that $MgSO_4$ can serve as an effective anticonvulsant countermeasure to nikethamide *in vivo*.

Comparison with previous studies

Our results align with and extend the existing literature on respiratory stimulants and anticonvulsant therapies. Nikethamide (also known as coramine) has historically been used to stimulate respiration in acute respiratory failure[3]. However, it is well documented that at high doses or with prolonged use, nikethamide and similar analeptics can provoke adverse effects such as tachypnea, convulsions, and even life-threatening respiratory paralysis[19-21]. The convulsive side effects we observed in control mice given high-dose nikethamide are consistent with these earlier reports. Previous animal studies have begun to elucidate nikethamide's neural effects: For instance, Qian *et al*[2] demonstrated that nikethamide's enhancement of respiratory rhythm in neonatal rat brainstems involves activation of 5-hydroxytryptamine (5-HT) 2A receptors, and additional work implicates gamma-aminobutyric acid(A)_A receptor modulation in nikethamide-induced respiratory changes[4]. These findings support the notion that nikethamide can broadly increase excitatory neurotransmission, which may underlie its seizure-inducing potential.

$MgSO_4$'s efficacy as an anticonvulsant, on the other hand, is well established in certain clinical contexts. It is the treatment of choice for eclamptic seizures in obstetric practice[7,8] and has been reported to exhibit anticonvulsant and neuroprotective properties in various models[5]. Our observation that $MgSO_4$ suppresses seizures is in line with these known anticonvulsant effects. To our knowledge, however, no prior studies have specifically examined $MgSO_4$ for preventing drug-induced convulsions from respiratory stimulants like nikethamide. Thus, our study fills an important gap by demonstrating that magnesium's protective action can be extended to this unique scenario. In contrast to some reports that magnesium therapy can ameliorate respiratory symptoms in COVID-19 patients (an effect that remains somewhat controversial)[13,14], our work focuses on magnesium's role in managing a serious side effect of a COVID-19 therapeutic. This distinct perspective underscores the innovative nature of our findings while remaining consistent with the general understanding that $MgSO_4$ is a broad-spectrum anticonvulsant agent.

Mechanistic interpretation

The protective effects of $MgSO_4$ observed in our study can be explained by known neurophysiological mechanisms. Nikethamide exerts its respiratory stimulant action by enhancing CNS excitatory pathways, but this same action can tip into pathological excitation at high doses. Pharmacologically, nikethamide is known to prolong the open state of neuronal sodium channels and to activate NMDARs in the brain. Excessive sodium influx and NMDAR activation lead to a cascade of neuronal hyperexcitation: Increased intracellular Ca^{2+} entry through NMDAR-associated channels triggers downstream effects such as the overproduction of nitric oxide (a potent vasodilator and neuromodulator), ultimately resulting in aberrant neural firing and convulsions[22-25]. This mechanism explains why an overdose of nikethamide can induce seizures even as it stimulates respiration.

The respiratory rhythm control center in the pre-Bötzinger complex (Figure 2) is modulated by multiple neurotransmitters, with 5-HT being the most important neurotransmitter[26,27]. Endogenous activation of 5-HT2A[28] receptors is necessary for the production of respiratory rhythm *in vitro*. Protein kinase C can antagonize the blockade of the endogenous activation network of 5-HT2A receptors. Endogenously activated 5-HT2A receptors regulate Na^+ conduction through the protein kinase C pathway to maintain this process[22,23]. Nikethamide alters the conformation of sodium ion channels and keeps them open for a long time, thereby altering the sodium ion current and affecting sodium ion distribution, leading to the induction of epilepsy and convulsions[24,25].

Magnesium ions is a natural noncompetitive antagonist of NMDARs that mainly blocks calcium ions (Ca^{2+}) influx through voltage-gated channels (Figure 3). By regulating the activity of Na^+-Ca^{2+} channels in neurons, $MgSO_4$ injection has a good antagonistic effect on seizures induced by nikethamide[12-14]. By limiting calcium entry and stabilizing neuronal membranes, magnesium can prevent the excitotoxic escalation that leads to seizures. Additionally, Mg^{2+} has a general inhibitory influence on neurotransmission—for example, it can dampen excessive release of excitatory transmitters and interfere with the sodium-calcium exchange cycle that sustains high-frequency neuronal firing. In our experiment, these properties of magnesium almost certainly underlie the prolonged seizure latency, reduced seizure severity, and extended seizure duration observed in the treated mice. Essentially, $MgSO_4$ raises the seizure threshold by inhibiting the neuronal hyperexcitation induced by nikethamide. This mechanistic interpretation is supported by the observed dose-response: Higher doses of magnesium produced deeper CNS depression (*e.g.* sedation and decreased locomotor activity), indicating a stronger blockade of excitatory neural activity[29,30]. However, this also reflects the drug's narrow therapeutic window–the same mechanisms that quell seizures can, in excess, suppress normal neural function (leading to respiratory and circulatory depression at very high levels of magnesium). Overall, the interplay between nikethamide and magnesium in our study highlights a classic excitatory-inhibitory counterbalance in neuropharmacology: Nikethamide drives neural activity up, while magnesium pushes it down, and at appropriate dosing, magnesium successfully restrains nikethamide's overstimulation of the CNS.

Clinical implications

Our findings have direct implications for improving the safety of COVID-19 treatments involving respiratory stimulants. Severe COVID-19 pneumonia[15-18] often leads to acute hypoxemic respiratory failure, partly due to dysregulated pulmonary vascular function and inflammation in the lungs (*e.g.* impaired hypoxic pulmonary vasoconstriction and widespread alveolar damage)[31-33]. In such cases, respiratory stimulants like nikethamide have been employed to drive ventilation in an attempt to counter profound hypoxia[3,34]. Nikethamide may offer transient benefits when respiratory muscle function remains partly intact[34,35], but its utility is severely limited by the risk of precipitating convulsions at higher doses or prolonged use. Our study suggests a solution to this dilemma: Co-administering $MgSO_4$ could prevent or attenuate nikethamide-induced seizures, thereby enabling the therapeutic use of nikethamide in critical COVID-19 patients who might otherwise be prone to drug-provoked convulsions. In practical terms, $MgSO_4$ could be considered as a prophylactic adjunct in COVID-19 cases where nikethamide or similar respiratory analeptics are indicated for refractory hypoxemia.

Several factors make $MgSO_4$ an attractive option in this context. It is inexpensive, widely available, and familiar to clinicians due to its long-standing use in conditions like preeclampsia, where it is valued for both efficacy and safety when used within the proper dose range[6,36]. Importantly, magnesium's mode of action (sedation and seizure prevention) addresses exactly the side effect that limits nikethamide's application. By mitigating convulsions, magnesium might expand the viable dosing range of nikethamide, potentially improving oxygenation in COVID-19 patients without inducing neurological complications. However, clinicians must also be mindful of $MgSO_4$'s narrow therapeutic window [37]. The sedative effects we observed at high doses in mice parallel known risks in humans–excessive magnesium can cause respiratory depression, loss of deep tendon reflexes, and cardiac arrhythmias or arrest if levels become toxic[7]. Thus, any clinical protocol emerging from this research would need to balance efficacy with careful monitoring (*e.g.* frequent reflex checks and magnesium level measurements) to avoid iatrogenic harm. In summary, incorporating $MgSO_4$ as a countermeasure could substantially enhance the safety profile of nikethamide therapy for COVID-19-related respiratory failure, but it would require judicious dosing and monitoring in the clinical setting.

Limitations and future directions

While promising, these results should be interpreted in light of several limitations. First, our study was conducted in a mouse model, and the extent to which the findings translate to humans remains uncertain. Mice were administered acute doses of nikethamide and $MgSO_4$; this controlled scenario may not capture the full complexity of COVID-19 patients who could have co-morbidities, ongoing inflammation, and concurrent medications. The number of animals per group was limited, which, despite yielding statistically significant outcomes, suggests that further studies with larger sample sizes are warranted to confirm the robustness of the protective effect. Additionally, we focused on short-term outcomes (seizure latency, duration, and survival in the acute phase after nikethamide exposure). We did not assess longer-term neurological status or potential cumulative toxicity, which could be relevant if $MgSO_4$ were to be used repeatedly or continuously in a clinical setting.

Mechanistically, we inferred magnesium's site of action (NMDAR blockade and general CNS depression) from existing knowledge, but we did not directly measure neural activity markers in our experiments. Future research could include electrophysiological studies or neurochemical assays (for example, measuring glutamate release, calcium influx in neurons, or electroencephalogram monitoring during seizures) to directly validate the proposed mechanism of seizure suppression by magnesium in the context of nikethamide. It would also be valuable to explore optimal dosing strategies–for instance, whether a moderate dose of $MgSO_4$ might suffice to prevent seizures without causing undue sedation, or if fractionated dosing could maintain protection with lower peak magnesium levels.

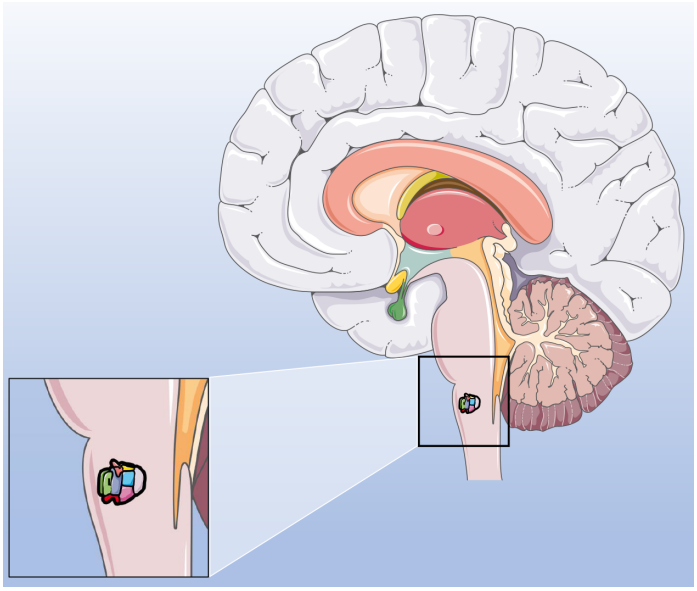


Figure 2 The position of the pre-Bötzinger complex. The pre-Bötzinger complex is located in the ventrolateral medulla oblongata.

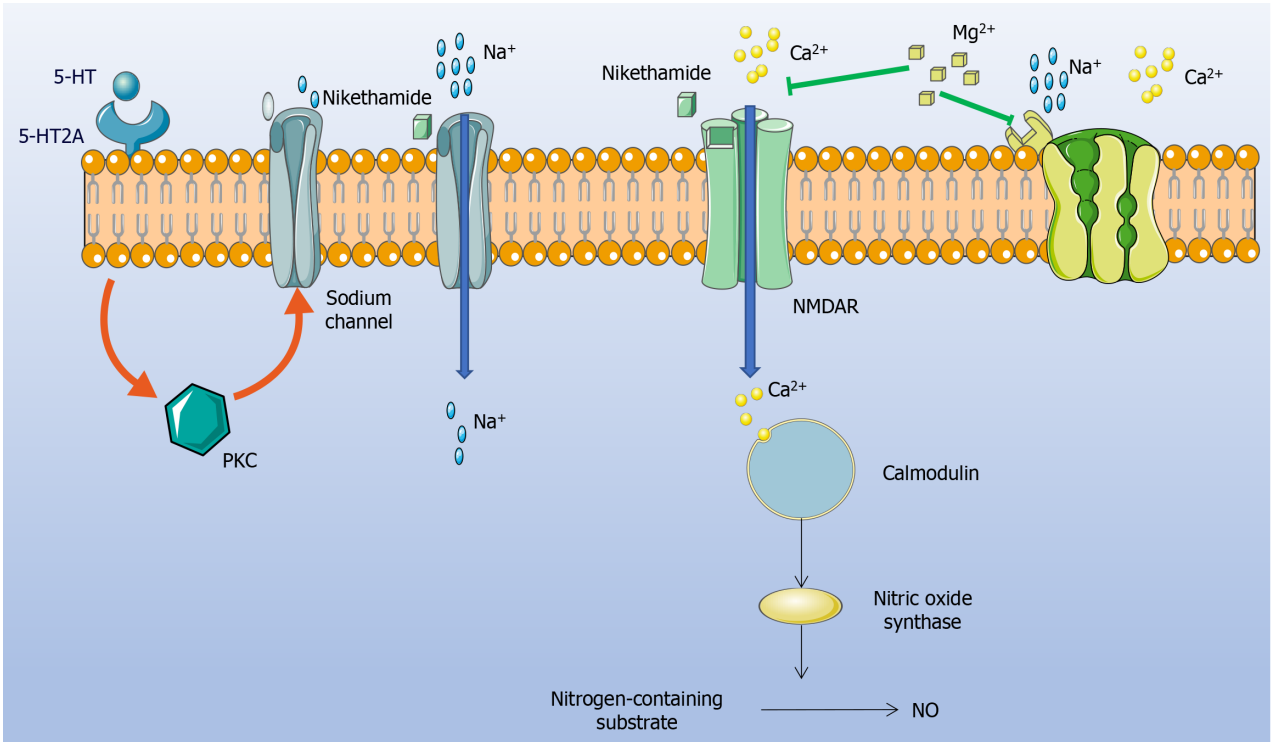


Figure 3 The molecular mechanism of the respiratory rhythm control center in the pre-Bötzinger complex. The 5-hydroxytryptamine (5-HT) is an important neurotransmitter, can activate protein kinase C (PKC) by binding to the 5-HT2A receptor. PKC further regulates the conduction of sodium ions, which is essential for maintaining respiratory rhythm. The activation of N-methyl-D-aspartate receptors (NMDARs) leads to the influx of calcium ions (Ca^{2+}) into neurons. Calmodulin is a calcium-binding protein, forms a complex with intracellular Ca^{2+} and further activates nitric oxide (NO) synthase to generate large amounts of NO. Magnesium ions (Mg^{2+}) is a natural antagonist of NMDARs, can block Ca^{2+} influx through voltage-gated channels and thus antagonize NMDAR activation. Therefore, Mg^{2+} can be used as an antagonist to treat seizures caused by glutamate. Ca^{2+}: Calcium ions; Mg^{2+}: Magnesium ions; Na^{+}: Sodium ions; NO: Nitric oxide; PKC: Protein kinase C; 5-HT: 5-hydroxytryptamine.

Another important direction is to evaluate $MgSO_4$ in more clinically relevant models. This could include studies in larger animals or in rodent models that mimic COVID-19 pneumonia (*e.g.* using viral infection or inflammatory agents to induce lung injury and hypoxemia) to see if magnesium retains its protective effect against nikethamide-induced seizures under those conditions. Ultimately, a carefully controlled clinical trial in COVID-19 patients receiving nikethamide (or analogous respiratory stimulants) could be conducted to determine safety, optimal dosing, and efficacy of magnesium co-therapy. Such trials should closely monitor not only respiratory parameters and seizure occurrence but also potential side

effects of magnesium, ensuring patient safety.

CONCLUSION

In conclusion, our work provides a proof-of-concept for using $MgSO_4$ to broaden the therapeutic utility of nikethamide by mitigating its most serious side effect. Further research and development are needed to transition these findings from bench to bedside, but the therapeutic implications are significant: If successful, this strategy could enhance treatment options for severe COVID-19 and improve outcomes by safely addressing refractory hypoxemia without added risk of seizures. The balance of efficacy and safety will be the guiding principle in these future investigations.

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FOOTNOTES

Author contributions: Xu DJ was responsible for data curation and writing of the original draft; Zhong Q was responsible for methodology and software; Wang GT was responsible for formal analysis and resources; Lu X was responsible for conceptualization, writing, reviewing and editing; all the authors participated in drafting the manuscript, and all the authors read, contributed to, and approved the final version of the manuscript.

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Institutional animal care and use committee statement: All animal experiments were reviewed and approved by the Institutional Animal Care and Use Committee of Taizhou University. The study followed the national and institutional guidelines for the care and use of laboratory animals, ensuring ethical handling and welfare throughout the experimental procedures.

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ORIGINAL ARTICLE

Basic Study

Effect of alpha-tocopherol and OTR-4131 on muscle degeneration after rotator cuff tear in rats: An experimental protocol

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Abstract

BACKGROUND

Massive rotator cuff tears (RCTs) result in impaired shoulder function and quality of life. These tears lead to structural changes in the rotator cuff muscles, which compromise recovery after repair and increase re-tear rates.

AIM

To investigate the potential inhibitory effects of alpha-tocopherol (vitamin E) and OTR-4131 on muscle atrophy, fatty infiltration, and fibrosis in rotator cuff muscles following a massive RCT using a Wistar rat model, and establish a standardized methodology for evaluating potential therapeutic agents.

METHODS

This protocol outlines a controlled animal study using 40 male Wistar rats, rando-

mized into five groups. The experimental groups will receive either systemic administration of alpha-tocopherol or local administration of OTR-4131 *via* intramuscular injection into the supraspinatus and infraspinatus muscles. Two sham groups will receive systemic and local saline injections respectively, while a control group will undergo no intervention. The interventions will be administered after surgical transection of the supraspinatus and infraspinatus tendons. Outcomes will be assessed *via* wet muscle weight measurements, muscle fiber diameter, fatty infiltration percentage, and fibrosis evaluation using histological methods.

RESULTS

The study anticipates that alpha-tocopherol and OTR-4131 will reduce muscle atrophy, fatty infiltration, and fibrosis compared to control and sham groups, supporting their potential protective role in rotator cuff muscle degeneration.

CONCLUSION

The results are expected to improve the understanding on the role of alpha-tocopherol and OTR-4131 in rotator cuff muscle protection after massive RCT and may serve as a foundation for further preclinical and clinical research aimed at improving rotator cuff repair outcomes.

Key Words: Alpha-tocopherol; OTR-4131; Rotator cuff tears; Experimental protocol; Muscle atrophy; Fatty infiltration

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Core Tip: This experimental protocol outlines a novel approach to investigating the use of therapeutic agents, following massive rotator cuff tears in a rat model. By systematically assessing muscle atrophy, fatty infiltration, and fibrosis, this study aims to establish a standardized methodology for evaluating potential therapeutic agents. The findings from this protocol could provide critical insights into muscle preservation strategies, potentially informing future preclinical and clinical interventional studies for rotator cuff repair.

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INTRODUCTION

Massive rotator cuff tears (RCTs), especially in elderly patients, are associated with significant functional decline and reduced quality of life. The management of this group of patients is challenging in orthopaedics[1]. Patient-related factors as well as factors related to the individual characteristics of the tear play a role in treatment decision making. Patient-related factors include patient age, presence of comorbidities, and level of functional demands, while the individual characteristics of the tear include parameters such as the size and chronicity of the tear, as well as the presence of fatty infiltration and/or muscle atrophy[2]. Following a massive RCT, the rotator cuff muscles undergo pathological changes, including fibrosis, atrophy, and fatty infiltration, which compromise postoperative functional recovery[3]. Muscle atrophy and fatty infiltration have been attributed to both disuse-related degeneration and mechanical factors, such as increased tension on the suprascapular nerve due to tendon retraction[4,5]. Additionally, oxidative stress has been implicated as a key contributor to rotator cuff muscle degeneration and atrophy following tendon rupture[6,7].

Biomechanical and histological investigations in animal models have confirmed that muscle atrophy and fatty infiltration, hallmark features of chronic massive RCT, significantly impair myotendinous unit function[3,8] Clinically, these degenerative changes are associated with poorer outcomes as well as increased rerupture rates after repair[9,10]. The poor prognosis of chronic massive RCT with concomitant significant muscle degeneration has led many surgeons to consider alternative methods of surgical treatment, such as latissimus dorsi tendon transfer or superior capsular reconstruction[11,12].

Recent research has increasingly focused on identifying factors that inhibit or decrease the rate of progression or even reverse muscle atrophy and fatty infiltration in patients with massive RCTs. This study protocol introduces a novel approach by investigating the potential therapeutic effects of two agents, alpha-tocopherol and the synthetic heparan sulfate mimetic OTR-4131, on mitigating muscle atrophy, fatty infiltration, and fibrosis in rotator cuff muscles following massive RCT. The protective and regenerative properties of alpha-tocopherol have been reported in studies involving the muscles of the lower limbs[13,14]. This effect is attributed to its ability to mitigate oxidative stress and prevent proteolytic degradation. Its antioxidant properties protect muscle cells from damage induced by reactive oxygen species while preserving the integrity of the extracellular matrix. Additionally, alpha-tocopherol downregulates the expression of genes involved in muscle proteolysis and promotes the expression of protective proteins, such as heat shock protein 72, which

play a crucial role in muscle preservation and recovery. Similarly, OTR-4131 has demonstrated protective and regenerative effects in muscle injury models, likely due to its ability to stabilize the extracellular matrix, prevent excessive proteolytic activity, and enhance the bioavailability of growth factors essential for tissue repair[15].

This experimental protocol aims to outline the methodology for evaluating the effects of alpha-tocopherol and OTR-4131 on muscle atrophy and fatty infiltration following a massive RCT in a rat model, with the hypothesis that these treatments will mitigate these pathological changes and yield favorable histological and morphological outcomes compared to controls.

MATERIALS AND METHODS

Ethics approval

Approval for this randomized, prospective experimental protocol was granted by the Ethics and Bioethics Committee of the School of Medicine, Aristotle University of Thessaloniki. All procedures will comply with the revised European and National Regulations (European Community Council directive 86/609/EEC; Presidential Degree 56/2013). The study protocol is prepared according to the ARRIVE guidelines 2.0 for reporting animal research[16]. The study is conducted under the supervision and contribution of a veterinarian, who will be responsible for observance of the rules of hygiene in the premises and the rules of acclimatization, protection, and nutrition of the experimental animals.

Study design and population

For the purposes of this research, an experimental control trial will be conducted using 40 male Wistar rats aging 12 weeks. Wistar rats are selected as animal models due to their widespread use in musculoskeletal and rotator cuff research. This animal model has already been validated in previous studies for replicating degenerative changes similar to those seen in massive human RCTs[8,17]. Its significant similarities to humans in terms of the shoulder joint anatomy (presence of coracoacromial arch, presence of suprascapular and subscapular tendons) and the degenerative changes that occur in the rotator cuff muscles following the occurrence of massive RCTs make it an appropriate and reliable model for this type of experimental research[18]. To minimize inter-animal variability in response to interventions, rats will be weight-matched (± 10%) at the time of randomization. We used the 12-week age threshold, as this corresponds to early adulthood in rats[19]. At this developmental stage, rats have completed sexual maturation, offering a stable musculoskeletal and hormonal environment suitable for modeling degenerative changes following massive RCTs. Male rats will be chosen to avoid overlapping hormone-related confounding factors in the experiment.

Only animals suitable for surgical procedures and meeting laboratory animal care guidelines will be included. Exclusion criteria will apply to rats with pre-existing musculoskeletal abnormalities, conditions affecting the rotator cuff or surrounding musculature, signs of illness, stress, or injury during preoperative assessment, failure to recover appropriately from anesthesia, or postoperative complications. Additionally, any condition compromising animal welfare or the validity of experimental results will lead to exclusion as determined by the veterinary team. The rats will be housed in pairs of two in each cage, to minimize the chances of aggressive behavior, under a controlled temperature of 18-22 °C and humidity of 55%-60%, with controlled 12-hour intervals of light and darkness, at the accredited animal facility of the laboratory of anatomy, Histology and Embryology of Aristotle University of Thessaloniki's veterinary school (accreditation number EL54BIO23). They will undergo a one-week acclimatization period before the initiation of the experiment to minimize stress and ensure baseline stability. Rats will have free access to water and food. No antibiotics will be administered, and male rats are chosen to avoid the effects of hormone-related factors in the experiment.

The rats will undergo surgical dissection of the rotator cuff of the right shoulder and will be randomized into five experimental groups by a computer algorithm (Google computer random number generator): (1) A group consisting of 8 male rats, in which no intervention, surgical or pharmaceutical, will be performed (Control Group); (2) A group consisting of 8 male rats, in which alpha-tocopherol will be administered systematically *via* intramuscular injection into the gluteus muscles on the first postoperative day and every 7th day thereafter for up to 8 weeks postoperatively (alpha-tocopherol study group); (3) A group consisting of 8 male rats, in which an equal dose of isotonic saline solution will be administered *via* the same route at the same time points during the experiment (alpha-tocopherol sham group); (4) A group consisting of 8 male rats, in which the agent OTR-4131 will be administered as a solution with a dose of 10 μL and a concentration of 1 μg/10 μL *via* intramuscular injection in each of the supraspinatus and infraspinatus muscles (OTR-4131 study group); and (5) A group consisting of 8 male rats, in which an equal dose of isotonic saline solution will be administered by intramuscular injection into each of the supraspinatus and infraspinatus muscles (OTR-4131 sham group). The endpoint of the study for all groups is set at 8 weeks after the initial surgery, at which time tissue harvesting and outcome assessments will be performed. An 8-week monitoring period was chosen as it represents a well-established timeframe for evaluating chronic degenerative changes following rotator cuff injury in rodent models[20].

To minimize potential confounders, all rats will be allocated randomly to their cages and coded by an individual not participating otherwise in the study. The same person will assign the coded animals to the surgeons and prepare the treatment solutions, ensuring that the surgeons remain blinded to the treatment groups. To maintain consistency in surgical technique, all procedures will be performed by the same two surgeons. Additionally, the pathologist conducting the histological analyses will be blinded to the group allocation of the specimens. These measures are designed to reduce bias and enhance the reliability of the study results. Humane endpoints for the study will include monitoring for signs of severe distress, pain, systemic illness, or infection. Animals will be observed twice daily for the first 48 hours postoperatively and once daily thereafter. Specific signs monitored include abnormal feeding behavior, reduced activity, signs of severe pain (*e.g.*, vocalizations, hunching, or guarding), and evidence of infection such as redness, swelling, discharge, or

delayed wound healing at the surgical site. In cases where infection is detected, appropriate veterinary care will be provided. If the condition does not improve despite intervention or results in significant distress, the animal will be humanely euthanized to prevent unnecessary suffering. The study process flowchart is presented in Figure 1. An overview of the experimental protocol is presented in Figure 2.

Sample size justification

The sample size was calculated using data from previous studies on muscle fiber thickness (cross sectional area), which is an indirect histological marker for assessing muscle atrophy[21,22]. To detect a difference of 835 μm^2 in mean muscle fiber thickness between the control group (mean ± SD: 1838 ± 644 μm^2) and the injected group (mean ± SD: 2673 ± 421 μm^2), it was estimated that 8 rats per group would be needed. Taking into account a mortality loss rate of 10%, the final sample size was set at 9 rats per group. The power was set at 80% and the significance level at 5%. Sample size was calculated using the statistical program G*Power 3.1.9.4.

Intervention agents and administration

Alpha-tocopherol: Alpha-tocopherol (Vitamine E Nepalm, 100 mg/2 mL, Greece) will be dissolved in 0.1 mL of sesame oil (Chemco Sesame Seed Oil Refined, 100 mL, Athens, Greece). Systemic administration of alpha-tocopherol *via* intramuscular injection into the muscles of the back (gluteal region) will be performed, in a dosage of 1000 IU/kg/week. The intramuscular route was selected to ensure slow systemic release and reliable bioavailability. This administration dosage and type has been used in previous animal studies with rats investigating muscle tissue protection and antioxidant effects and has proven to be effective and safe[23,24]. Moreover, the dosage intake is well below the toxicity levels[25].

OTR-4131: The heparan sulfate mimetic OTR-4131 (provided by OTR3 Company, Paris, France) will be used in the form of intramuscular injection. The injection will take place immediately after the surgically induced RCT. A single injection will be used for each muscle, namely the supraspinatus and infraspinatus. To evaluate its effect 10 µL of 1 µg/µL solution will be used. The injection volume and concentration were determined based on prior studies in rats, where comparable local administration supported muscle regeneration without systemic toxicity[15,26].

Experimental procedure

At T0 (day 0), rats in the control and study groups will undergo general anesthesia, with the administration of ketamine (50 mg/kg) and xylazine (5 mg/kg). The surgical area will be shaved and sterilized with an antiseptic solution. Each rat will be placed in the prone position and secured on a surgical board to ensure stability during the procedure. A longitudinal skin incision, approximately 1-1.5 cm in length, will be made over the right shoulder joint and careful dissection through the subcutaneous tissue will be performed to expose the underlying structures. The deltoid muscle will be identified, and its fibers separated longitudinally. Similarly, muscle fibers from the lateral trapezoid muscle will also be separated longitudinally, in line with the spinus process, for adequate visualization of supraspinatus and infraspinatus tendons. The supraspinatus and infraspinatus muscles and their tendons will be identified, with the supraspinatus muscle-tendon unit located cranially, in the supraspinous fossa, and the infraspinatus located more caudally, in the infraspinous fossa (Figure 3). For experimental purposes, both tendons will be transected creating a model for studying RCTs. A Penrose drain will be placed around the tendon edges to prevent spontaneous reattachment. The deltoid and trapezoid muscles will be repositioned and the skin incision will be closed with fine sutures. The procedures aim to simulate the pathological environment of massive RCTs. In the OTR-4131 group, during the operation, the animals will receive an intramuscular injection in the supraspinatus and infraspinatus muscles of either OTR-4131 solution (OTR-4131 study group) or corresponding saline solution (OTR-4131 sham group). In the alpha-tocopherol group, the animals will receive after the operation an intramuscular injection of either alpha-tocopherol (study group) into the gluteus muscle or corresponding saline solution (control group) starting on operation day and subsequently every 7th day until the 8th postoperative week. After surgery, animals will be released into their housing cages and will be monitored daily for 8 weeks.

At T1 (day 56), a reoperation under similar anesthesia will be performed for the purpose of harvesting the infraspinatus and supraspinatus tendon-muscle units. A new incision will be made in line with the previous shoulder incision and extended medially toward the scapula. The subcutaneous tissue will be carefully dissected to reveal the trapezoid and deltoid muscles, which will again be split longitudinally in line with spinus process and retracted, in order to visualize the full extent of the infraspinatus and supraspinatus muscles (Figure 4). Both muscles will be identified and subperiosteally elevated from their origin on the scapula. Following muscle harvesting, the muscle-tendon specimens will be weighed, placed in a wooden tongue depressor with their edges pinned down to secure muscles length retention (Figure 5) and wrapped in saline-soaked gauze to maintain their moisture. After transport to the pathology laboratory, the specimen will be cryopreserved in liquid nitrogen (-196 °C). This rapid freezing will ensure the tissue's structural integrity by preventing ice crystal formation that could otherwise damage the muscle. Following cryopreservation, 1 mm-thick sections will be cut from the specimen and stored for further histological analysis to assess the fat infiltration and muscle atrophy. The pathologist who will perform the measurements will be blinded regarding the origin of each specimen. This study does not constitute a clinical trial; therefore, clinical trial number is not applicable.

Euthanasia

After the second surgical procedure and tissue harvesting, rats will be euthanized by use of a CO_2 euthanasia chamber, following the American Veterinary Medical Association Guidelines for the euthanasia of animals: 2020 edition[27].

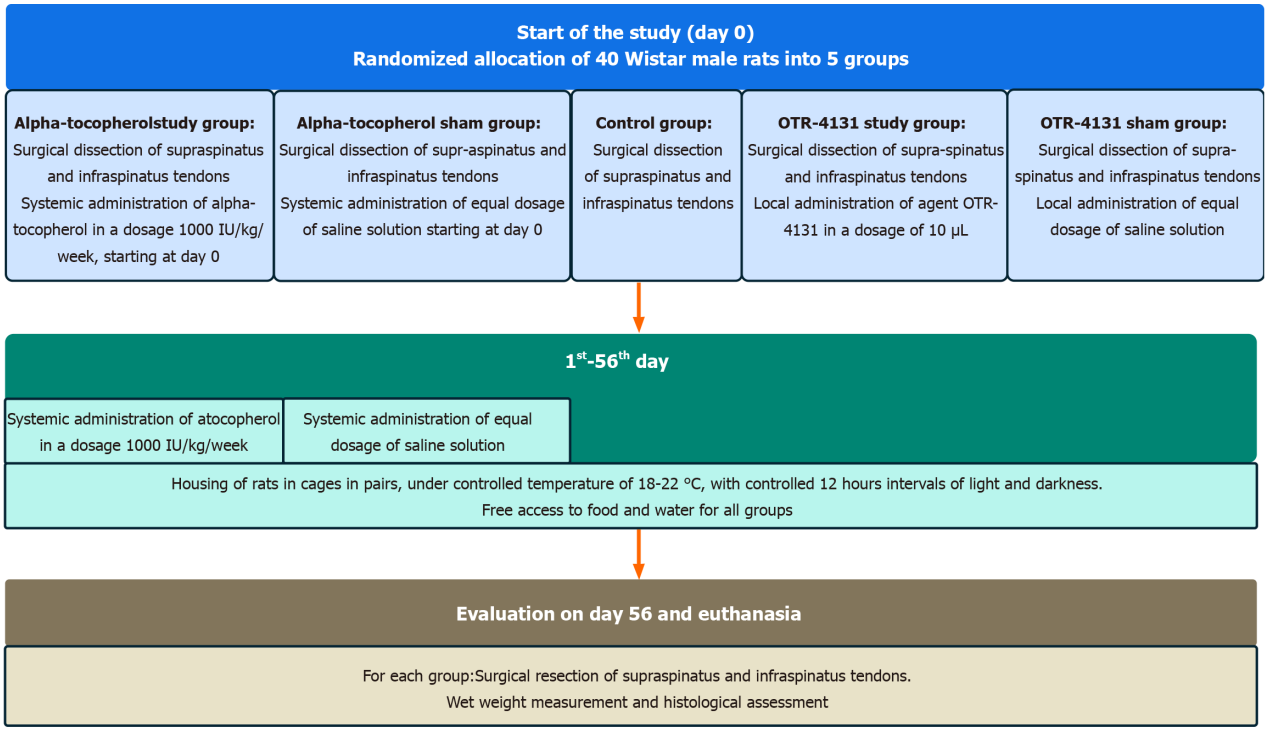


Figure 1 Study process flowchart.

Outcomes

Muscle atrophy of the rotator cuff muscles will be assessed by the following methods: (1) Measurement of muscle wet weight, immediately after tissue harvesting[28]; and (2) Following specimen fixation in 4% formalin, measurement of the mean diameter of the muscle fibers in transverse cross-section (cross sectional area) will be performed after hematoxylin-eosin staining and with use of Image J software (Image J, MD, United States)[3,28]. The presence and degree of fatty infiltration will be assessed by measuring the mean percentage distribution of adipocytes in images obtained after oil red staining and use of Image J software[8,17]. Finally, the presence and degree of fibrosis will be assessed by measuring the average percentage distribution of fibrous tissue between muscle bundles after Masson trichrome staining and use of Image J software[8].

Statistical analysis

The primary outcomes are continuous quantitative variables. Normality of data distribution will be assessed using the Kolmogorov-Smirnov test. For variables demonstrating a normal distribution, group comparisons will be performed using an independent samples *t*-test to evaluate differences in mean values between the intervention and control groups. In cases where the data do not conform to a normal distribution, the Mann-Whitney *U* test will be employed as a non-parametric alternative. Statistical analysis will be conducted using SPSS software (IBM Corp., Armonk, NY, United States), and a *P* value of < 0.05 will be considered indicative of statistical significance.

RESULTS

As this study is an experimental protocol, no data are currently available. The intervention groups are expected to exhibit better preservation of muscle structure, with higher muscle wet weight and larger muscle fiber diameter compared to the sham groups. Histological analysis with hematoxylin and eosin staining may indicate improved muscle fiber integrity, suggesting reduced atrophy in the treatment groups. Fatty infiltration is anticipated to be less pronounced in the alpha-tocopherol and OTR-4131 groups, as assessed by oil red O staining. In contrast, the sham groups may demonstrate increased intramuscular fat deposition, indicative of progressive muscle degeneration. Fibrosis, evaluated using Masson's trichrome staining, is expected to be lower in the treatment groups, particularly in the OTR-4131 group, as this agent is hypothesized to stabilize the extracellular matrix and enhance the bioavailability of growth factors. The control group, in which no surgical intervention or pharmacological treatment will occur, is expected to maintain normal muscle morphology without signs of atrophy, fatty infiltration, or fibrosis. Comparisons between the intervention, sham, and control groups will provide insight into the extent of muscle degeneration following a massive RCT and the protective effects of the tested agents. The results of this study will contribute to a better understanding of the progression of muscle degeneration after RCTs and the potential therapeutic applications of alpha-tocopherol and OTR-4131. Detailed findings, including histological and morphological outcomes, will be presented in future publications.

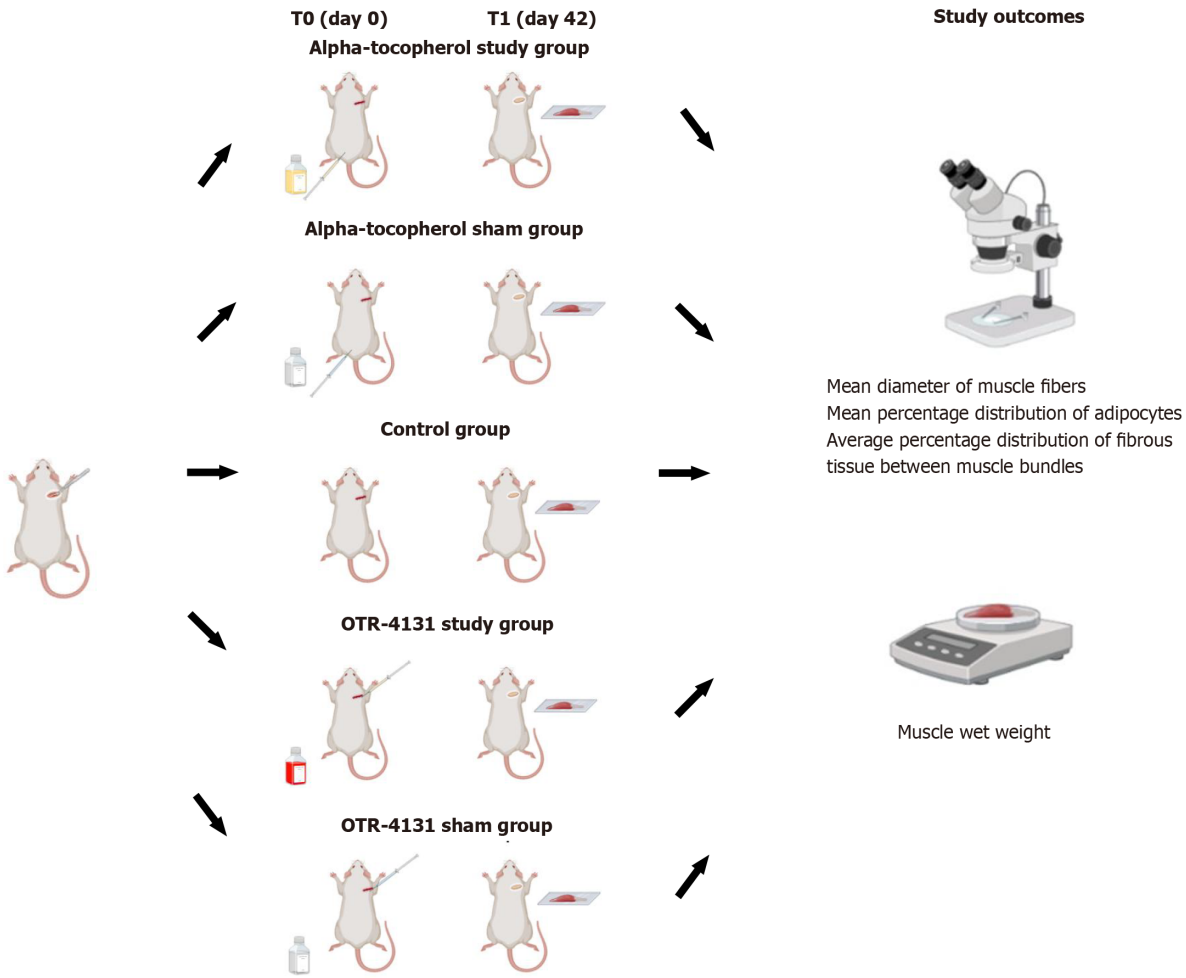


Figure 2 An overview of the experimental design. This figure was created with BioRender.com.

DISCUSSION

RCTs are among the most common causes of shoulder pain and disability, with an incidence of approximately 30% in patients over 60 years[22]. They impose a significant economic burden, with more than 75000 surgeries performed annually[21]. Moreover, massive RCTs are associated with functional impairments, including reduced shoulder abduction, decreased range of motion due to stiffness, and diminished shoulder strength[29]. Depending on the size of the tear, RCTs are classified as small, medium or massive. Although no clear definition of massive RCT has been established in the literature, criteria such as a tear greater than 5 cm in maximum diameter and a tear involving two or more tendons are commonly used[2,30]. After a massive RCT, several pathologic changes occur in the rotator cuff muscles, including fibrosis, muscle atrophy and fatty infiltration, that can lead to poor recovery after surgery and increased rate of recurrence[31].

An increasing research interest has emerged towards investigation of interventions that mitigate the development of muscle atrophy, fatty infiltration and fibrosis after repair of massive RCTs. Several studies have examined the contribution of oxidative stress to muscle homeostasis, as well as muscle injury under different circumstances (crushing, overuse, muscle unloading and disuse, age)[32-35]. Oxygen free radicals are produced both at rest and during muscle contraction. Although low and normal levels of oxygen free radicals are necessary for normal force production in skeletal muscle, high levels can lead to oxidative damage to lipid and myocyte proteins[34]. In addition, oxygen free radicals regulate a number of signaling pathways as well as the expression of many genes which results in increased expression of proteolytic enzymes, increased activation of proteases and inhibition of protein synthesis in muscle. This combination of proteolysis and reduction in protein synthesis leads to loss of muscle protein[36,37]. The regulation of other gene products, such as antioxidant enzymes, stress proteins and mitochondrial electron transport proteins, is also affected by oxidative stress[36]. As a response to oxidative stress, myocytes produce antioxidant enzymes, such as peroxisome dismutase, catalase, glutathione peroxidase, γ-glutamylcysteine synthase and heme oxygenase-1, which do not only neutralise redundant oxygen free radicals, but also intervene in the various stages of muscle regeneration: They influence the inflammatory response after injury, enhance the viability and proliferation of muscle satellite cells and myoblasts, and influence their differentiation[38]. Finally, antioxidant enzymes also regulate the processes that accompany muscle regeneration, they induce angiogenesis and reduce fibrosis[33]. The role of oxidative stress has also been studied in rotator cuff pathology and appears to be involved in both the degeneration observed at the enthesis level and the degeneration and atrophy of rotator cuff muscles[39-41].

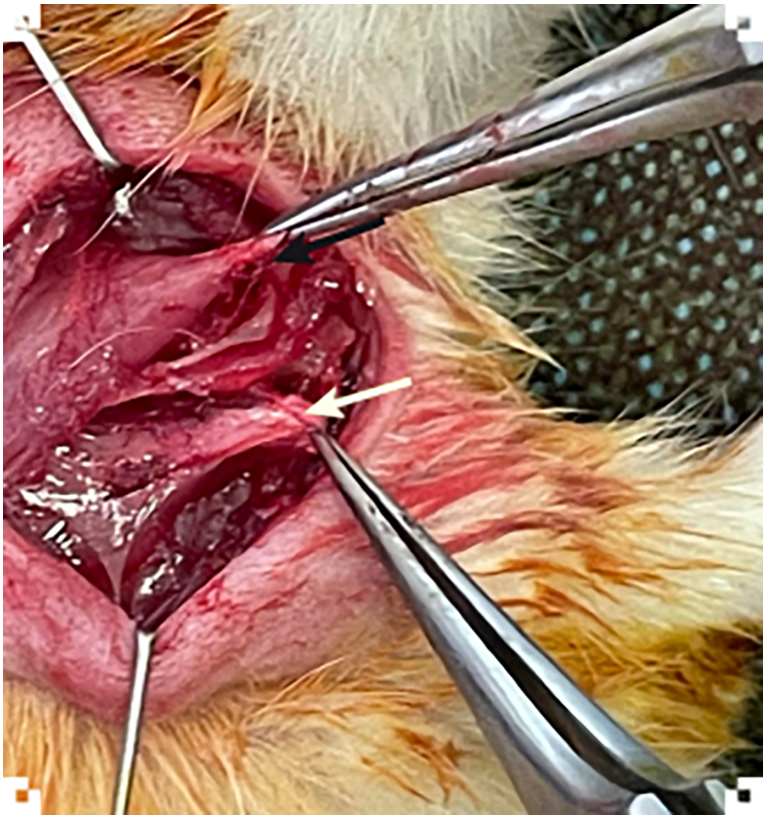


Figure 3 Image from the pilot surgery showing the identification of the supraspinatus (black arrow) and infraspinatus tendons (white arrow).

Apha-tocopherol is a water-soluble vitamin that has been extensively studied for its antioxidant properties[42]. Apha-tocopherol reduces oxidative stress by inducing an increase in the concentration of endogenous antioxidant enzymes and by reducing the levels of lactate in the blood, glutathione S-transferase, by-products of lipid peroxidation (thiobarbituric acid reactive substances) in plasma and liver, and levels of carbonyl protein in liver and muscles. In addition, alpha-tocopherol suppresses the expression of mediators of inflammation including nuclear factor-κB, tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-8, inducible nitric oxide synthase, cyclooxygenase 2 and the transcription factor signal transducer and activator of transcription 3. Finally, alpha-tocopherol regulates the expression of hypoxia-inducible factor-1, which is also associated with inflammation[43]. The effects of alpha-tocopherol in skeletal muscle have also been investigated under various circumstances, including diabetes, exercise, ischemia-reperfusion and muscle atrophy induced by limb unloading. Studies in animal models have shown that exogenous vitamin E supplementation enhances antioxidant defenses, reduces oxidation, suppresses oxidative stress, increases protein synthesis, and reduces protein degradation[14,44]. Servais *et al*[14] studied the effect of alpha-tocopherol on muscle atrophy induced by disuse in the gastrocnemius muscle in Wistar rats and found that it displays a protective effect through regulation of proteolytic enzyme gene expression and to a lesser extent through its antioxidant activity. Finally, Morikawa *et al*[45] studied the effect of another antioxidant, vitamin C, on degeneration of the rotator cuff tendon in in an experimental model of superoxide dismutase 1-deficient mice with induced supraspinatus tendon entheses degeneration. The authors found improvement in the histological parameters examined (collagen fiber orientation, chondrocyte number and percentage of oriented chondrocytes, polarized light refraction area and metachromatic area).

Heparan sulfate proteoglycans (HSPGs) are complex molecules consisting of a protein core attached to heparan sulfate glycosaminoglycan chains. These biomolecules play a critical role in the regulation of growth factors and the bioavailability of heparin-binding proteins, which are vital to tissue repair and regeneration[46]. Among these, fibroblast growth factor-2 (FGF-2) has garnered significant attention for its involvement in muscle regeneration. FGF-2 forms a ternary complex with its receptors and HSPGs, which is essential for proper FGF-2 signaling during muscle repair[47]. Increased expression of FGF-2 is noted in skeletal muscle during regeneration, and its infusion has been shown to enhance muscle recovery in models of injury and disease, such as dystrophic and reinnervated muscles[48,49]. Conversely, inhibition of FGF-2 signaling can lead to impaired muscle repair, further highlighting the critical role of HSPGs in the regeneration process. Synthetic analogues of heparan sulfate, such as OTR-4131, have been developed to mimic the functions of natural HSPGs while offering additional benefits, such as increased resistance to enzymatic degradation. This resistance allows OTR-4131 to preserve the structural integrity of matrix proteins and protect growth factors from proteolytic breakdown. This property is crucial in muscle repair, as it creates a microenvironment conducive to tissue regeneration[50,51]. In muscle injury models, OTR-4131 has demonstrated its capacity to promote muscle regeneration by facilitating extracellular matrix remodeling and increasing the availability of growth factors like FGF-2. While other agents aimed at reducing fatty infiltration and muscle atrophy act through different pathways, OTR-4131's mechanism is unique in its

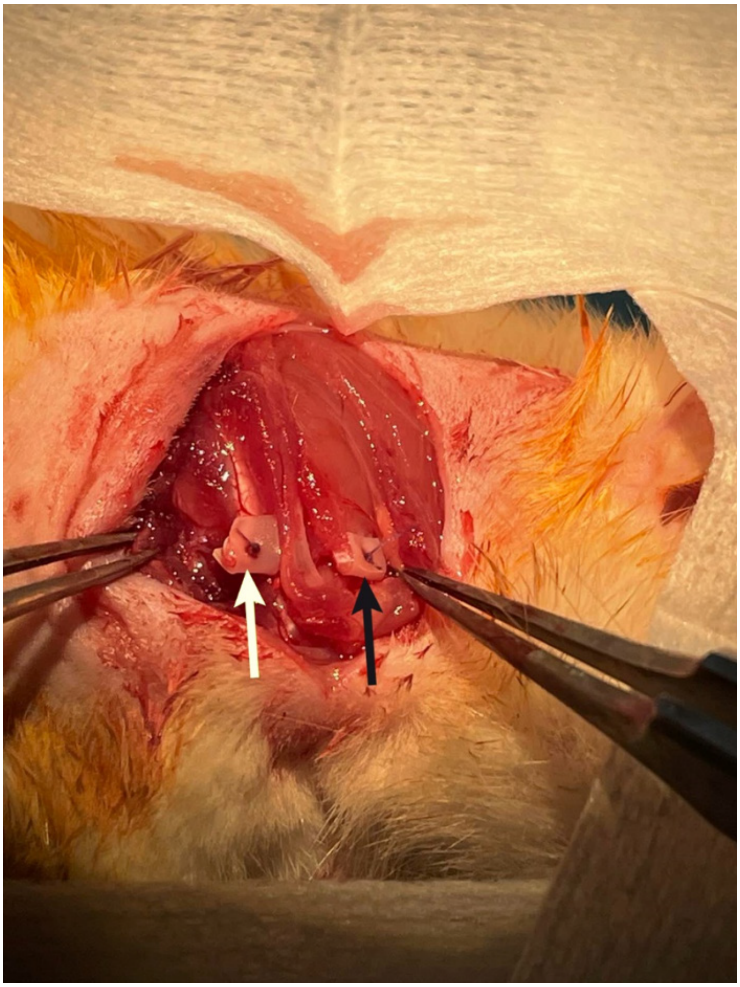


Figure 4 Image from the pilot surgery during the second procedure, illustrating the complete visualization of supraspinatus (black arrow) and infraspinatus (white arrow) muscles prior to harvesting.

focus on protecting the extracellular matrix and enhancing growth factor-mediated repair[52,53].

In this experimental study, we hypothesized that administration of alpha-tocopherol or agent OTR-3141 affects the development of muscle atrophy and fatty infiltration after massive tear of the rotator cuff of the shoulder in an experimental Wistar rat model. The use of a rat model provides a controlled and reproducible system, leveraging similarities in musculoskeletal structure and healing mechanisms that can be extrapolated to other species, including humans. However, species-specific differences in muscle physiology, immune response, and metabolic pathways may limit the direct generalizability of the results. While the experimental conditions allow precise assessment of the interventions' effects, these controlled environments may not fully replicate the complexity of clinical scenarios. If successful, the results could inform further preclinical studies in larger animal models and, eventually, clinical trials in humans to assess the translational relevance of these findings.

The present study presents specific limitations. First, although the anatomy and function of the rotator cuff muscles in rats resemble those of humans, interspieces differences may limit the interprentation of the results[54,55]. Secondly, there are inherent limitations, as in most experimental studies, regarding the exact dosage as well as the route of administration of the investigated substance, as these parameters cannot be directly extrapolated to humans. Thirdly, RCTs in animals show an increased healing potential which contrasts with the corresponding findings in humans[55]. An additional limitation is the difference in the rupture site, as in humans, RCTs usually happen after a closed injury to a tendon that probably already has some degree of degeneration, in contrast to the surgical transection of the tendon that is performed in this experiment. Finally, the safety and possible long-term side effects of the administered substance cannot be assessed, as all animals will be sacrificed at the end of the experimental study.

CONCLUSION

In summary, this study protocol explores the effects of alpha-tocopherol and the synthetic heparan sulfate mimetic OTR-4131 on muscle atrophy and fatty infiltration following massive RCTs. Both agents are expected to offer unique mechanisms of action, with alpha-tocopherol focusing on mitigating oxidative stress and regulating the expression of various genes, while OTR-4131 aims to protect the extracellular matrix and enhance growth factor bioavailability. By

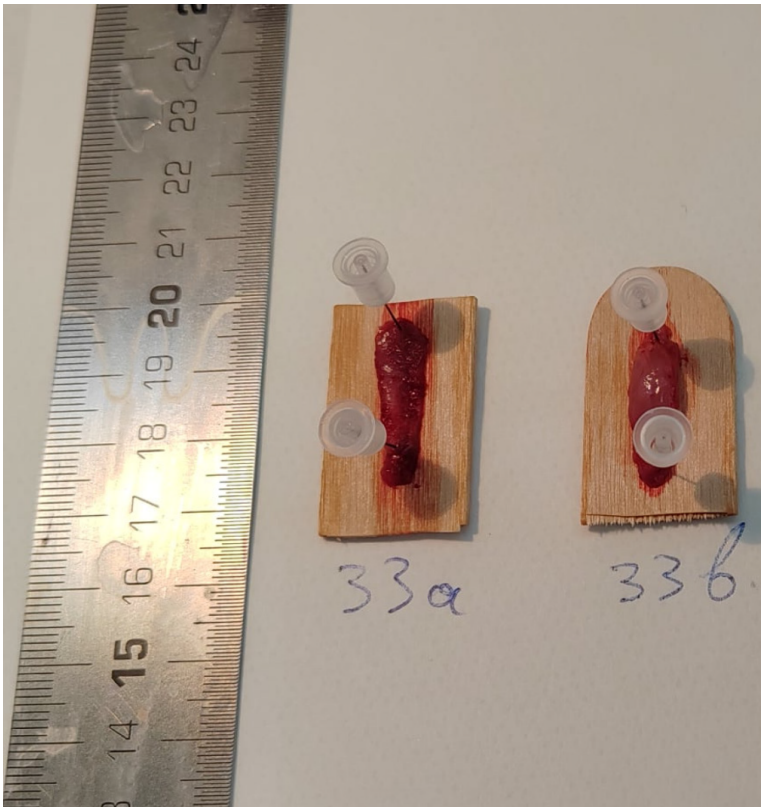


Figure 5 Specimens of infraspinatus (left) and supraspinatus (right) muscle units obtained during the pilot surgery.

investigating these agents separately, we hope to uncover their potential to mitigate muscle degeneration after massive RCT. The findings from this study could lead to more effective therapeutic strategies for patients suffering from rotator cuff injuries, ultimately enhancing their quality of life and functional outcomes.

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FOOTNOTES

Author contributions: Stamiris S, Stamiris D, and Sarris I conceived and designed the experimental study; Stamiris S, Stamiris D, and Bekiari C developed the study protocol and supervised its scientific integrity; Stamiris S, Stamiris D, and Anestiadou E performed the pilot surgical procedures; Cheva A and Loukousia A provided methodological input for histological and pathological assessments and critically revised the manuscript; Potoupnis M, Papavasileiou K, Tsiridis K, and Sarris I critically revised the study protocol for clinical relevance, contributed to manuscript drafting, and ensured scientific accuracy; Stamiris S and Anestiadou E wrote the first draft of the manuscript; all authors participated in reviewing, editing, and finalizing the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Institutional animal care and use committee statement: The research protocol was reviewed and approved by Ethics and Bioethics Committee of the School of Medical, Aristotle University of Thessaloniki.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: All data are available upon request.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

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SYSTEMATIC REVIEWS

Imaging findings of irritable bowel syndrome patients, and the diagnostic value of irritable bowel syndrome: A systematic review

Hyder Osman Mirghani

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal (FGITD) disorder, the diagnosis is based on Rome Criteria and other subjective tools. Because IBS overlaps with other FGITD and organic diseases, and the subjective tools do not apply to patients with cognitive decline, objective diagnostic tools are important in this category of patients.

AIM

To discuss the role of imaging in IBS diagnosis.

METHODS

We systematically searched three databases for articles published in the English language with no limitation to a specific period. The literature search was conducted in June and July 2024. The keywords used are IBS and functional bowel disorders, computed tomography, Magnetic Resonance Imaging, functional brain magnetic resonance imaging (MRI), and static brain MRI, and were linked with the terms "AND" and "OR". Out of the 679 articles, 578 remained after duplication removal. However, 50 full texts were used in the review.

RESULTS

Magnetic resonance imaging is superior due to its sensitivity, lack of radiation exposure, and lack of need for bowel preparation. Patients with IBS had smaller colonic and rectal volumes compared to healthy controls and functional constipation. Dynamic and static Magnetic Resonance Imaging of the brain showed increased activity, thinning, and increased volumes in specific areas of pain modulation. The above abnormalities are not uniform and vary significantly according to the type of IBS, the duration and intensity of symptoms, gender, and culture.

CONCLUSION

Magnetic resonance imaging shows smaller colonic and rectal volumes, and

increased activity, thinning, and increased volumes in specific areas of pain modulation. Large trials incorporating all above limitations are needed.

Key Words: Irritable bowel syndrome; Diagnosis; Magnetic resonance imaging; Ultrasound; Computed tomography

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Core Tip: Irritable bowel syndrome (IBS) is a prevalent brain-gut axis disorder, however, the diagnosis is based mainly on Rome Criteria which concentrates on the gastrointestinal tract with ignorance of the brain-gut axis. Furthermore, the Rome criteria are not suitable for patients with cognitive decline. Therefore, tools to address the above diagnostic gaps are highly relevant. In this review, we gave a broader insight into the role of abdominal and brain imaging in diagnosing IBS. The findings, the difference between diarrhea-predominant and constipation-predominant IBS, gender, geography, and cultural background, and the pros and cons of different imaging were discussed.

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INTRODUCTION

Irritable bowel syndrome (IBS) is among the most prevalent disorders of gut-brain cross-talk. The diagnosis of IBS is based largely on the Rome Criteria which are subjective and were developed in the Western countries. Therefore, they cannot be generalized to other parts of the world with different cultures[1].

Due to its chronic nature, its mental and organic impact, and the high prevalence, IBS socioeconomic burden is high, and its effects on the patient's quality of life are significant. In addition, the issue of IBS is dynamic and the understanding of the syndrome is rapidly changing because of the recent advances in relevant clinical research[2]. The prevalence of IBS varies significantly and depends on the methods of diagnosis, Geography, and culture. The Rome Foundation Global Study reported a prevalence of 10.1% and 3.8% when using Rome III, and Rome IV respectively. Importantly, the change in the dynasty of symptoms, the suggestion by the Rome IV Criteria to include the gut-brain interaction, and the overlap with other functional gastrointestinal syndromes have encouraged research in this field[2-4].

ROME 1V Criteria are more restrictive, less likely to diagnose unspecific symptoms, and milder for IBS. Therefore, they are more helpful in tertiary care centers, unlike the ROME III Criteria. Other limitations of the ROME Criteria are overlaps with organic diseases including chronic overlapping pain conditions[5], inflammatory bowel disease[6], and endometriosis, which are concerning[7]. In addition, some nations are less likely to express pain (Asians) bloating/distension. Therefore, IBS could be underestimated[8]. Similarly, the distorted body image and self-criticism created by IBS were thought to mediate the association between IBS, anxiety, and depression[9].

IBS encompasses a wider spectrum of gastrointestinal, extraintestinal, and psychological comorbidities. Because of this, other methods incorporating features other than stool consistency and forms are needed[10].

IBS is a chronic burdensome disorder that is usually misdiagnosed as another condition leading to delayed diagnosis and treatment. The delayed diagnosis of IBS substantially disturbs the quality of life of patients and increases the healthcare cost[11]. Positive diagnostic methods rather than the reliance on exclusion and ROME Criteria are highly needed for a better understanding of the disease and the introduction of multimodal treatment[12].

Because of the established association between IBS, psychological distress, and organic disease, imaging is justifiable in selected patients. Likewise, IBS patients ≥ 50 years old are at an increasing risk of dementia[13], and Rome Criteria might not be applicable among patients with cognitive decline. On the other hand, The United States, and United Kingdom suggested no radiological imaging for IBS diagnosis unless red flags are present. The radiological procedure depends on the most likely alternative diagnosis[14] because evidence shows that colonoscopy, barium enema, and ultrasound yield is low regarding structural changes (diverticulosis, inflammatory bowel disease, and colorectal cancer)[15]. Likewise, psychological stress could affect gut function and brain visceral sensitivity which is the case of IBS[16]. Functional imaging including magnetic resonance imaging (fMRI) and positron emission tomography (PET) significantly advanced our knowledge about gut-brain interaction in particular among patients with IBS. An interesting study used functional near-infrared spectroscopy to assess brain activity among patients with functional dyspepsia, IBS, and healthy control subjects in response to food images. The authors concluded that there was higher prefrontal cortex activity among patients with functional dyspepsia than among their IBS counterparts[17]. Therefore, imaging including abdominal ultrasound, computed tomography (CT), and MRI (abdominal or brain diffusion) could be justifiable in selected patients with cognitive decline and alarm features, in contrast to the subjective Rome Criteria. The current review aimed to discuss the role of imaging in IBS diagnosis.

MATERIALS AND METHODS

Setting

The current diagnosis of IBS with the ROME Criteria with the reliance on abdominal pain, stool form, and consistency has several limitations because several nations are less likely to express pain but fullness/bloating. In addition, IBS is a wider disease with internal and extra-intestinal symptoms and a great overlap with psychological disorders. Furthermore, ROME Criteria are not working among patients with cognitive decline.

This review was conducted in June and July 2024 with strict adherence to the PRISMA Guidelines to fulfill the objectives which are the role of imaging including ultrasound, CT, and MRI in IBS diagnosis.

Inclusion criteria

The inclusion criteria were Cross-sectional studies, retrospective and prospective studies, randomized trials, and case-control studies conducted on humans were approached. The studies were included if they used abdominal ultrasound, CT, and MRI to diagnose IBS. In addition, brain MRI, structural, and function among patients with IBS were approached.

Exclusion criteria

Case studies, opinions, editorials, and protocols without data were not. Barium studies, radionuclide studies, and colonoscopies were not included. Brain imaging was confined to MRI, therefore, CT brain with its different modalities was also excluded.

Outcome measures

The outcome measures were colonic diameters and transit time, and the static and dynamic changes of the brain MRI.

Literature search

We searched PubMed/MEDLINE, Google Scholar, and Cochrane Library for articles assessing the role of imaging as a diagnostic measure for IBS. The literature search was limited to the articles published in the English language with no limitation to a specific period. The keywords IBS and functional bowel disorders, CT, MRI, functional brain MRI, and static brain MRI were used and linked with the terms "AND" and "OR". The total hits in the above databases were 679 articles, and 578 remained after duplication removal. In the current review, 50 full texts were screened and used in the introduction and article text (Figure 1).

Data extraction

An Excel sheet was used to extract the author's name, year and country of publication, type of study, age, gender, number of participants, and the main results of the imaging procedure (Table 1).

Risk of bias assessment: We used the Newcastle Ottawa Scale to assess the quality of the included studies[18] (Table 2).

RESULTS

Characteristics of the included studies

The current review results were based on 14 studies, 7 studies were from Europe, 4 from Asia, two were published in Canada, and one from the United States. The studies included 1104 participants, and the majority were females. All the studies were observational studies (11 case-control and 3 were cross-sectional) with good quality (Figure 1, Tables 1 and 2).

DISCUSSION

Abdominal imaging changes in IBS

Colonic volume and transit time: MRI showed low colonic volume and rapid transit time among patients with IBS compared to chronic constipation and healthy control subjects[19] supporting a previous study conducted by Lam *et al* [20] who found higher ascending colon volume in functional constipation. More studies confirmed the above findings and attributed the findings to increased sensitivity to colon distention in patients with IBS because both constipation and diarrheal IBS had increased rectal sensitivity and less call for stool[21-24]. Importantly, there is substantial intra and inter-individual variation that should be controlled for before reaching a firm conclusion[25]. In addition, the colonic volume changes are not uniform through IBS spectra, Pritchard *et al*[21] observed a rise in ascending colon volume and a decrease in the descending colon following a meal in constipation-predominant IBS and healthy subjects suggesting a retrograde movement from the left colon[26], the reverse happen later. By contrast, the retrograde movement is not observed in diarrheal-predominant and mixed IBS[27]. Similarly, MRI showed smaller rectal volume among patients with IBS suggesting an increased tone in the resting state[28].

The current evidence of low colonic volume among patients with IBS is promising for the classification of colonic disorders. Future research to investigate whether patients with larger colonic diameters respond better to prokinetics or

Table 1 Basic characteristics and imaging results among patients with irritable bowel syndrome, mean ± SD

Ref.	Country	Study design	Sample size	Age/years	Females, %	Main result
Klinge *et al* [19], 2022	Denmark	Case-control	20	25-53	76%	Low colonic volume and rapid transit time among IBS patients compared to chronic constipation
Lam *et al*[20], 2016	United Kingdom	Case-control	48	27-53	91.3%	Higher ascending colon volume in functional constipation compared to IBS patients
Pritchard *et al*[21], 2014	United Kingdom	Case-control	50	39 ± 13	58.7%	Less ascending colon postprandial volume and high descending colon volume among IBS compared to healthy controls
Di Palma *et al* [28], 2011	Italy	Case-control	40	31 ± 7	66.7%	Rectal volume was smaller among IBS patients
Nilsson *et al* [34], 2015	Denmark	Cross-sectional	25	Not mentioned	All males	No inter-individual and intra-individual variability in colonic volume MRI
Grinsvall *et al* [38], 2021	Sweden	Case-control	354	27.9 ± 9.9	All females	Low grey matter volume in the posterior insula and superior frontal gyrus with high grey matter volume and cortical thickness in the somatosensory cortex and subcortical regions
Blankstein *et al*[39], 2010	Canada	Case-control	27	30.85 ± 8.9	All females	Increased gray matter in hypothalamus among patients with IBS, and anterior midcingulate cortical thinning
Chua *et al* [40], 2017	Taiwan	Case-control	69	36.7 ± 7.7	All females	Supramarginal cortex, middle frontal cortex, and left cuneus showed cortical thinning in IBS patients with a negative correlation with the disease severity
Jiang *et al* [42], 2013	United States	Case-control	266	34.72 ± 11.12	84.6%	No difference in cortical thickness between IBS patients and control subjects. Cortical thickness decreases in the bilateral subgenual anterior cingulate cortex, and increases in the somatosensory and primary motor cortex among women with IBS
Mao *et al*[43], 2020	China	Cross-sectional	68	Not mentioned	Diarrhhea predominant subjects	Enlarged caudate nucleus and thalamus, and altered hemispheric asymmetries among diarrhea-predominant IBS patients
Chen *et al* [44], 2011	Canada	Cross-sectional	26	20-54	All females	Mean fractional anisotropy was observed in IBS patients in the fornix and external capsules
Zhao *et al* [45], 2018	China	Case-control	30	77.5 ± 6.3	20%	Gray matter volume is low in occipital and frontal lobes, limbic and hippocampus, and high in angular and temporal gyrus, and insula
Icenhour *et al* [50], 2017	Sweden	Case-control	61	32-36	All females	Resting-state functional connectivity is reduced in the amygdala and insula in IBS patients
Guleria *et al* [51], 2017	India	Case-control	20	30.5	All males	Homeostatic emotions, autonomic responses to pain, and affective motivation differ in IBS patients compared to controls

IBS: Irritable bowel syndrome; MRI: Magnetic resonance imaging.

laxatives. MRI studies could help further the classification of patients and treatment guidance[27,28]. In addition, the separation of the colonic content (gas, fluid, or solid) using postprocessing of MRI could be helpful for the individualization of therapy (drug/diet)[29]. However, the current evidence was based on observational studies with female predominance which are more prone to bias. In addition, the MRI is not cost-effective and is not available in the primary care setting.

Regarding the colonic transit time, less transit time was reported among IBS compared to functional constipation, however, the study was performed after laxative stimulation and not under normal conditions[20]. A previous study[30] used radiopaque markers and found low transit time among patients with IBS compared to patients with diarrhea and constipation. Radiopaque markers and colonic scintigraphy although useful, radiation exposure is a big limitation[31].

Other attractive imaging are ultrasound and CT which can provide structural evidence. Ultrasound studies on IBS patients showed increased gallbladder and colon contractility with impaired pyloric and stomach contraction and transit, hyperechoic rectum with acoustic shadow is characteristic[32]. However, ultrasound is operator–dependent and is not sensitive to colonic volume evaluation, and CT radiation exposure is a major limitation[33]. Therefore, MRI is more attractive in the diagnosis of IBS and functional constipation, because it is sensitive, no need for bowel preparation, and no radiation exposure (a big advantage since most IBS patients are females of reproductive age)[34].

The diagnostic value of brain imaging changes in IBS patients

The gut-brain interaction: The pathophysiology of IBS is complex where gastrointestinal tract (GIT) symptoms are induced by any combination of visceral hypersensitivity, motility disorders, disturbance in mucosa and immunity, and altered gut microbiota diversity and function[35]. Interoceptive signals originate from the GIT and memories for them are extensively modulated by cognition, emotion (depression and anxiety), and motivational factors. Therefore, the

Table 2 Risk of bias assessment of the included studies

Ref.	Selection bias	Comparability bias	Outcome	Total score
Klinge *et al*[19], 2022	3	1	3	7
Lam *et al*[20], 2016	4	2	3	9
Pritchard *et al*[21], 2014	3	1	3	7
Di Palma *et al*[28], 2011	3	2	2	7
Nilsson *et al*[34], 2015	3	2	2	7
Grinsvall *et al*[38], 2021	4	2	3	9
Blankstein *et al*[39], 2010	3	2	3	8
Chua *et al*[40], 2017	3	2	3	8
Jiang *et al*[42], 2013	3	2	2	7
Mao *et al*[43], 2020	3	2	3	8
Chen *et al*[44], 2011	3	2	2	7
Zhao *et al*[45], 2018	3	2	3	8
Icenhour *et al*[50], 2017	3	2	3	8
Guleria *et al*[51], 2017	3	2	2	7

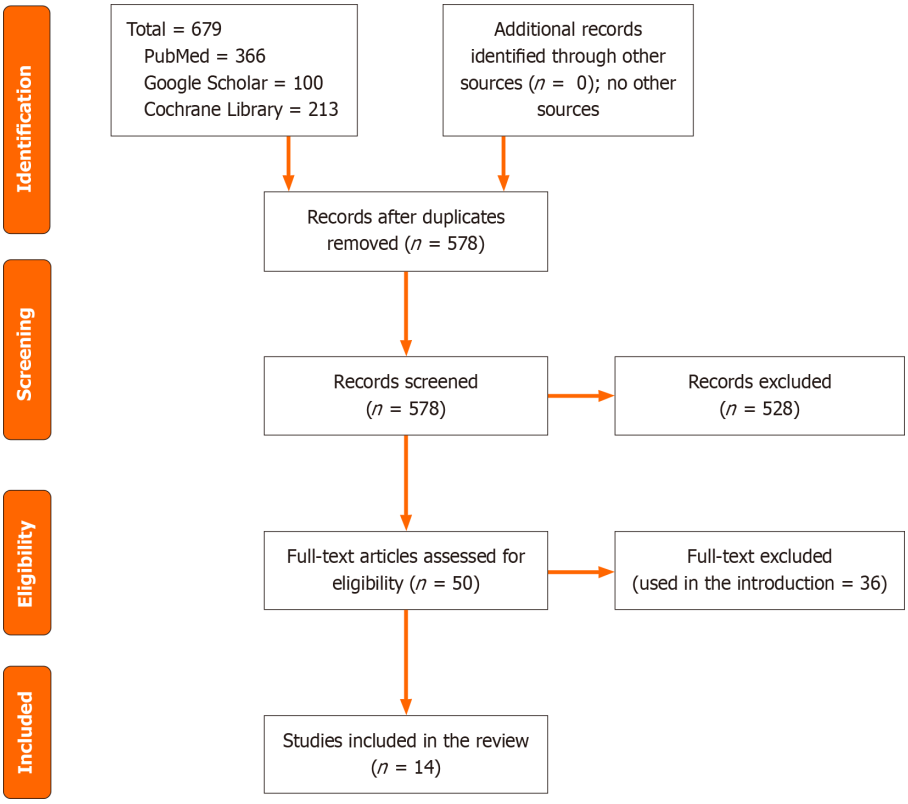


Figure 1 Literature search to retrieve articles assessing the role of imaging in the irritable bowel syndrome diagnosis (The PRISMA Chart).

pathophysiology is wide and involves the GIT (gut connectome), wide areas of the brain (brain connectome), and input from the autonomic nervous system, and neuroendocrine[36]. The multifactorial nature of IBS makes the diagnosis challenging, there is a need for objective measures to address the brain static and dynamic change to assist the diagnosis, suggest future research, and guide IBS therapy.

Rectal nociception and MRI brain abnormalities: The gut-brain connections are not only important in food digestion, but also related to mood disorders, stress, altered bowel motility, and abdominal pain, because of that rectal inflation

among patients with IBS activates the emotion arousal, attention, and visceral sensation areas of the brain[37].

Higher cortical thickness and grey matter volume in the somatosensory cortex and subcortical regions were found among women with IBS, the reverse was observed in the superior frontal gyrus and posterior insula[38]. Blankstein *et al* [39] used functional MRI and found high grey matter volume in the hypothalamus with thinning in the anterior midcingulate might be related to continuous stress and activation of the hypothalamic-pituitary-adrenal axis. Chronic abnormal input from the GIT or pre-existing brain abnormalities that predisposed to IBS could explain the findings. Importantly, Chua *et al*[40] confirmed the cortical thinning, but with a negative correlation with the duration and severity of abdominal pain. The contradiction in the above results could be explained by cultural and gender disparities in pain perception[41], people from the East are more tolerant of pain compared to their counterparts from the Western region and females tolerate pain more[42].

Enlarged caudate nucleus and thalamus were observed in diarrhea-predominant IBS with thalamic rightward asymmetries and leftward asymmetries in the caudate nucleus in contrast to the finding in the healthy controls[43]. Chen *et al*[44] conducted a study among IBS females and showed higher mean fractional anisotropy in the insula and fornix while matter compared to their counterparts without the syndrome. Zhao *et al*[45] conducted a study among elderly IBS patients, structural MRI, diffusion tensor imaging analysis, and Voxel-based morphometry studies supported by Blankstein *et al*[39] and Chen *et al*[44]. An important finding with clinical implication is the association between depression and similar cortical thinning observed in IBS, additionally, depression is prevalent among IBS patients[46,47]. Hence, some tricyclic antidepressants might be an effective therapy for IBS[48].

Brain resting state activity in IBS: The resting state brain activity among patients with IBS differs significantly from healthy volunteers, high activity resting state was observed in wide areas including the postcentral gyrus, frontal, and temporal lobe. In contrast, the cingulate and paracingulate gyrus showed decreased resting state activity. Importantly, resting-state functional connectivity is related to visceral sensitivity and symptom severity[49,50]. Interestingly, the brain activation is different in constipation and diarrheal-predominant IBS[51].

Only English literature should be included, and various screening criteria resulted in a small number of articles being included.

CONCLUSION

Patients with IBS had smaller colonic and rectal volumes compared to healthy controls and functional constipation. Dynamic and static MRI of the brain showed increased activity, thinning, and increased volumes in specific areas of pain modulation. High colonic diameter and decreased transit time detected by MRI are promising for the diagnosis of IBS due to its sensitivity, lack of radiation exposure, and lack of need for bowel preparation. Imaging could be beneficial for the diagnosis of IBS among patients with alarm symptoms and cognitive dysfunction because Rome Criteria are subjective and need patients' responses. Imaging results could direct response to specific IBS treatment (diet/medications). The above abnormalities are not uniform and vary significantly according to the type of IBS, duration, intensity of symptoms, gender, and culture. Because of that, high patient selection is needed. Large trials incorporating all IBS subtypes, both women and men and controlling for sociodemographic and cultural factors are needed.

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FOOTNOTES

Author contributions: Mirghani HO performed the conception and design of the study, the literature search, and the drafting, critical revision, and provided the final approval of the version to be published.

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Diagnostic methods for managing dry eyes

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Abstract

BACKGROUND

Dry eye disease (DED) represents a multifactorial condition characterized by ocular discomfort and visual disturbances. The management of DED relies heavily on accurate diagnosis to tailor effective treatments. Diagnostic approaches encompass both subjective and objective assessments.

AIM

To review the diagnostic methods used in the process of dry eye disease management.

METHODS

A comprehensive review of diagnostic approaches for dry eye was performed using scientific databases. Studies published within the last four years were considered. Studies were excluded if a full text was absent or the article was not written in English. Articles were assessed for relevancy, and a total of 107 studies were selected. The selection method used a systematic methodology, which guaranteed an exhaustive assessment of the diagnostic techniques reported in current literature. The study adheres to principles for systematic reviews ensuring

dependability and accuracy. The studies were assessed for emphasize on both novel traditional and diagnostic methods for dry eye disease management.

RESULTS

Key objective tests include tear break-up time, which evaluates tear film stability; fluorescein and lissamine green staining, which assess ocular surface damage and inflammation; tear osmolarity measurement, indicative of tear film quality; and tear volume assessment *via* Schirmer's test, which evaluates tear production. Advanced imaging techniques such as optical coherence tomography and meibography offer detailed anatomical insights into the ocular surface and meibomian glands, aiding in the diagnosis of underlying structural abnormalities. Moreover, emerging technologies such as matrix metalloproteinase-9 testing and inflammatory biomarkers provide additional diagnostic precision, particularly in identifying inflammatory components of DED.

CONCLUSION

Integrating a combination of subjective and objective diagnostic tools allows clinicians to comprehensively assess the condition, tailor treatment plans, and monitor therapeutic efficacy. Continued advancements in diagnostic technologies promise to enhance our understanding and management of this prevalent ocular condition.

Key Words: Dry eye syndrome; Diagnostic methods; Tear film stability; Ocular surface; Meibomian glands

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Core Tip: Keratoconjunctivitis sicca, or dry eye disease (DED), is a common ocular illness with different incidence rates worldwide. The complicated etiology of DED involves tear film instability and can cause pain, decreased vision, and ocular surface damage. Evaporative and aqueous-deficient dry eye have different causes. Differentiating between these types is often required for appropriate diagnosis and effective therapy. A detailed diagnosis is needed as Sjögren's syndrome, an autoimmune condition, is connected to a type of DED. Recent advances aim to standardize diagnosis and improve therapy by addressing the causes of DED.

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INTRODUCTION

Dry eye disease (DED), also known as dry eye syndrome (DES) or keratoconjunctivitis sicca (KCS), is a common ocular condition affecting millions globally, with prevalence rates ranging from 5% to 50%[1-3]. This multifactorial disease of the ocular surface causes discomfort and visual disturbances[4] and is more likely to be encountered in primary care settings rather than secondary or tertiary centers[5]. The tear film, which consists of mucin, aqueous, and lipid layers[6], can become unstable due to disruptions in the normal anatomy or physiology of these layers. This instability may result from qualitative or quantitative abnormalities in the tear film's aqueous, lipid, and mucin layers.

The 2017 DEWS II report redefined DED as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles"[7]. Ongoing Delphi analyses aim to enhance understanding of DED and establish a standardized framework for its diagnosis and management[8].

DED can result from reduced tear secretion by the lacrimal glands, increased tear evaporation, or the production of poor-quality tears. This tear instability can lead to ocular surface inflammation, damage, and abnormal nociception[9]. Symptoms include burning, foreign body sensations, blurred vision, and redness, which can cause discomfort and reduce work efficiency and quality of life[10]. Complications may include conjunctival scarring or corneal issues that can impair vision[11].

The primary roles of the aqueous component of the tear film are to lubricate the surface of the eye, remove unwanted objects or contaminants, and provide nourishment to the cornea, which lacks blood vessels (such as oxygen, inorganic salts, proteins, and glucose)[12]. Consequently, when these glands are not functioning properly, there is a decrease in the production of necessary fluids and other important substances required to maintain and protect the surface of the eye. This leads to dry eye and possibly severe damage to the eye's surface[13]. Dry eye is a prevalent ocular condition, with an estimated prevalence of 14% to 33% in adults, which tends to increase with age[14]. It is often accompanied by other ocular conditions, such as impaired vision[15]. The variation in the occurrence and frequency of dry eye in different regions of the world has been attributed, in part, to interracial variances across populations[16]. The preservation of clear vision and ocular comfort relies on the integrity and stability of the air-tear film interface, which serves as the principal refractive surface of the eye[17]. The more severe symptoms of DED are linked to reduced job productivity and activity

levels, both when comparing different individuals (cross-sectionally) and over time within the same person (intra-individually)[18].

DED is a diverse disorder with multiple poorly understood subcategories, broadly classified into aqueous-deficient and evaporative DED. Five distinct subgroups have been identified, each exhibiting substantial differences in demographics, symptoms, clinical signs, and associations with systemic diseases[19]. These include: (1) Sjögren's syndrome-related DED; (2) Non-Sjögren aqueous deficit; (3) Intrinsic evaporative DED; (4) Extrinsic evaporative DED, and (5) Mixed mechanism DED, aiding clinicians in implementing tailored treatment strategies[20,21]. Meibomian gland dysfunction (MGD) accounts for approximately 60% of DED cases, leading to a deficiency in tear film lipids and causing intrinsic evaporative DED. Conversely, extrinsic evaporative DED stems from environmental factors such as contact lens wear or ocular surface disorders. Sjögren's syndrome and other autoimmune conditions also play a significant role in aqueous-deficient DED[19]. The diagnosis of DED relies on meibography, lipid layer thickness evaluation, and evaporimetry, which help differentiate between subtypes and guide appropriate management[21].

Primary Sjögren's Syndrome (PSS) is a persistent condition characterized by symptoms of dryness in the mouth and eyes, as well as discomfort, exhaustion, anxiety, and despair. The Newcastle Sjögren's Stratification Tool may classify PSS patients based on the severity pattern of five significant symptoms[22]. Research revealed a higher prevalence of primary Sjögren syndrome in women compared to males. This condition is characterized by increased dryness, positive autoantibodies[23,24], and a higher likelihood of co-occurring primary biliary cholangitis (PBC) in adults. The presence of PSS influences the clinical characteristics of PBC[25]. Oral dryness is a prominent characteristic of Sjögren syndrome, a condition linked to a higher likelihood of developing oral disorders and a worse quality of life-related to oral health[26]. Sjögren's syndrome dry eye (SSDE) is a specific form of dry eye that differs from non-SSDE (NSSDE). It is a subtype of Sjögren's disease characterized by dry eye symptoms. Timely detection of SSDE is crucial as it might lead to significant complications. Nevertheless, differentiating between SSDE and NSSDE[27,28] remains challenging due to the same clinical signs.

KCS, sometimes referred to as NSSDE, is a prevalent disorder marked by persistent dryness and irritation of the eyes. NSSDE, in contrast to Sjögren's syndrome, has no connection to an autoimmune illness that impacts tear-producing glands[29]. Alternatively, it can be attributed to many causes, such as environmental influences, hormone fluctuations, certain drugs, and natural aging[30]. Common symptoms of this condition include enduring dryness, a sensation of grittiness, and a burning feeling in the eyes. Additionally, individuals may have impaired vision and heightened sensitivity to light. Possible treatment modalities encompass the administration of artificial tears, prescription drugs, and modifications in lifestyle, such as using humidifiers and evading arid surroundings[31]. Sjögren's syndrome is associated with digestive[32], dental[33-35], cardiovascular[36-39], and renal health consequences[40,41]. DED can also arise as a result of other ocular/systemic disorders such as thyroid eye disease[42] and fibromyalgia[43]. Views on the management of dry eye can diverge significantly[44], even among a specific subset of people. Extensive research conducted in India found that 39.62% of dry eye patients had evaporative dry eye, whereas 34.7% had aqueous deficient dry eye[45].

The successful management of DED depends on the precise diagnosis of the condition to determine the root cause and use the most suitable treatment method[46,47]. This study examines the existing diagnostic procedures for DED, including their advantages and disadvantages. It also discusses new approaches that are being developed and have the potential to enhance the diagnosis and treatment of DED.

MATERIALS AND METHODS

The authors searched the PubMed database using "Diagnostic methods in managing dry eyes" as keywords, as shown in Table 1.

Records that were not in the English language, lacked full text, and/or not relevant were further excluded as shown in the PRISMA[47] flowchart below in Figure 1. The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist (Figure 1).

RESULTS

The search string initially returned 914 records. Articles published more than 4 years ago and those not in English were excluded, leaving 199 records. Additionally, articles that were not available as free full text and lacked abstracts were excluded. This filtering process resulted in 199 articles, which were then retrieved by the authors. One publication was excluded because it had been retracted, another two on the basis of language, and 89 publications were not used because they were out of scope. A total of 107 publications were included in this review. A spread of the number of papers included as segregated by year of publication is shown in Figure 2[48-53].

DISCUSSION

Some of the diagnostic methods reviewed are shown in Table 2. Accurate diagnosis and management of dry eye are essential for improving patient quality of life[54]. While objective measurements are crucial for diagnosing and managing DED, subjective evaluations provide valuable insights into the patient's experience[55]. Subjective evaluations, which

Table 1 Search components and resulting algorithms

Search component	Keywords used
Diagnostic	"diagnosis" [MeSH Terms] OR "diagnosis" [All Fields] OR "diagnostic" [All Fields] OR "diagnostical" [All Fields] OR "diagnostically" [All Fields] OR "diagnostics" [All Fields]
Method	"methods" [All Fields] OR "methods" [MeSH Terms] OR "methods" [All Fields] OR "method" [All Fields] OR "methods" [MeSH Subheading] AND "manage" [All Fields]
Manage	"manage" [All Fields] OR "managed" [All Fields] OR "managements" [All Fields] OR "managements" [All Fields] OR "manager" [All Fields] OR "managers" [All Fields] OR "managers" [All Fields] OR "manages" [All Fields] OR "managing" [All Fields] OR "management" [All Fields] OR "organization and administration" [MeSH Terms] OR ("organization" [All Fields] AND "administration" [All Fields]) OR "organization and administration" [All Fields] OR "management" [All Fields] OR "disease management" [MeSH Terms] OR ("disease" [All Fields] AND "management" [All Fields]) OR "disease management" [All Fields])
Dry eye syndromes	("dry eye syndromes" [MeSH Terms] OR ("dry" [All Fields] AND "eye" [All Fields] AND "syndromes" [All Fields]) OR "dry eye syndromes" [All Fields] OR ("dry" [All Fields] AND "eye" [All Fields]) OR "dry eye" [All Fields])) AND ((ffrft[Filter]) AND (2020: 2024[pdat])).

Table 2 Diagnostic methods for dry eye curated from sampled records

Method	Ref.	Sample size	Diagnostic rubric
American-European consensus group classification criteria	Lee *et al* [48]	187 serum samples of age matched females	Authors suggest peptides treated with malondialdehyde increase the formation of autoantibodies, suggesting that they have diagnostic utility for primary Sjögren's Syndrome
Existing data analyses	Acar-Denizli *et al*[49]	12084 patients with ESSDAI scores	Combination patterns of two antibodies-anti-Ro/SSA and anti La/SSB was used to define Sjogrens syndrome
Machine learning algorithm using routine healthcare data	Dros *et al* [50]	1411 primary Sjögren's Syndrome patients and 929179 non-primary Sjögren's Syndrome patients	The task entailed employing logistic regression and random forest models for the purpose of categorizing patients. The models used characteristics such as age, gender, medical conditions, symptoms, medication prescriptions, and visits to general practitioners
Diagnostic criteria by Japanese research committee on severe cutaneous adverse reaction	Sotozono *et al*[51]	94 Stevens-Johnson syndrome and toxic epidermal necrolysis patients with severe ocular complications	The diagnostic criteria for ocular involvement in instances of Stevens-Johnson syndrome and toxic epidermal necrolysis include particular ocular abnormalities, such as the creation of pseudo-membranes and defects in the epithelium. These symptoms are regarded to be high-risk indicators for ocular complications
DryEyeRhythm mobile app	Inomata *et al*[52]	4454 individuals	The diagnostic rubric involved assessing subjective symptoms reported by the participants *via* the DryEyeRhythm app. The DryEyeRhythm is a mobile application that facilitates real-time monitoring of DED symptoms, allowing for remote symptom tracking and prompt intervention
Ultrasonographic techniques (grayscale and color Doppler sonography) and contrast-enhanced ultrasonography	Xu *et al*[53]	161 patients with primary Sjögren's Syndrome and 66 non primary Sjögren's Syndrome patients	The diagnostic approach entailed assessing the ultrasonographic characteristics of the parotid and submandibular glands. Ultrasonographic methods, encompasses grayscale and Doppler imaging, to evaluate lacrimal gland structure and vascularity in patients with DED

DED: Dry eye disease; ESSDAI: European league against rheumatism Sjogren's syndrome disease activity index.

include patient-reported symptoms and standardized questionnaires, are critical components in the diagnostic process [56].

Patient-reported symptoms and questionnaires

The diagnosis of DED is based mostly on the symptoms stated by the patient, as this gives direct insight into their experience. These symptoms include various discomforts, such as dryness, burning, stinging, grittiness, and vision problems[57]. Patients frequently complain of a chronic feeling of dryness or not enough tears, which can be made worse by external conditions like wind or low humidity[58]. Patients may also complain of these symptoms after prolonged screen time, which results in digital strain[59].

Clinical visits usually entail comprehensive patient discussions to assess these symptoms. Inquiries concerning symptoms' onset, length, frequency, and severity are among the detailed qualitative data collected. These data are essential for modifying treatment regimens to meet each patient's needs and tracking the long-term efficacy of treatments [60]. A thorough medical history is needed, as studies suggest a relationship between the white blood cell population and the symptoms experienced in DED patients[61]. Barrio-Cortes *et al*[62] concluded that other comorbidities positively correlated to the likelihood of patients presenting for treatment.

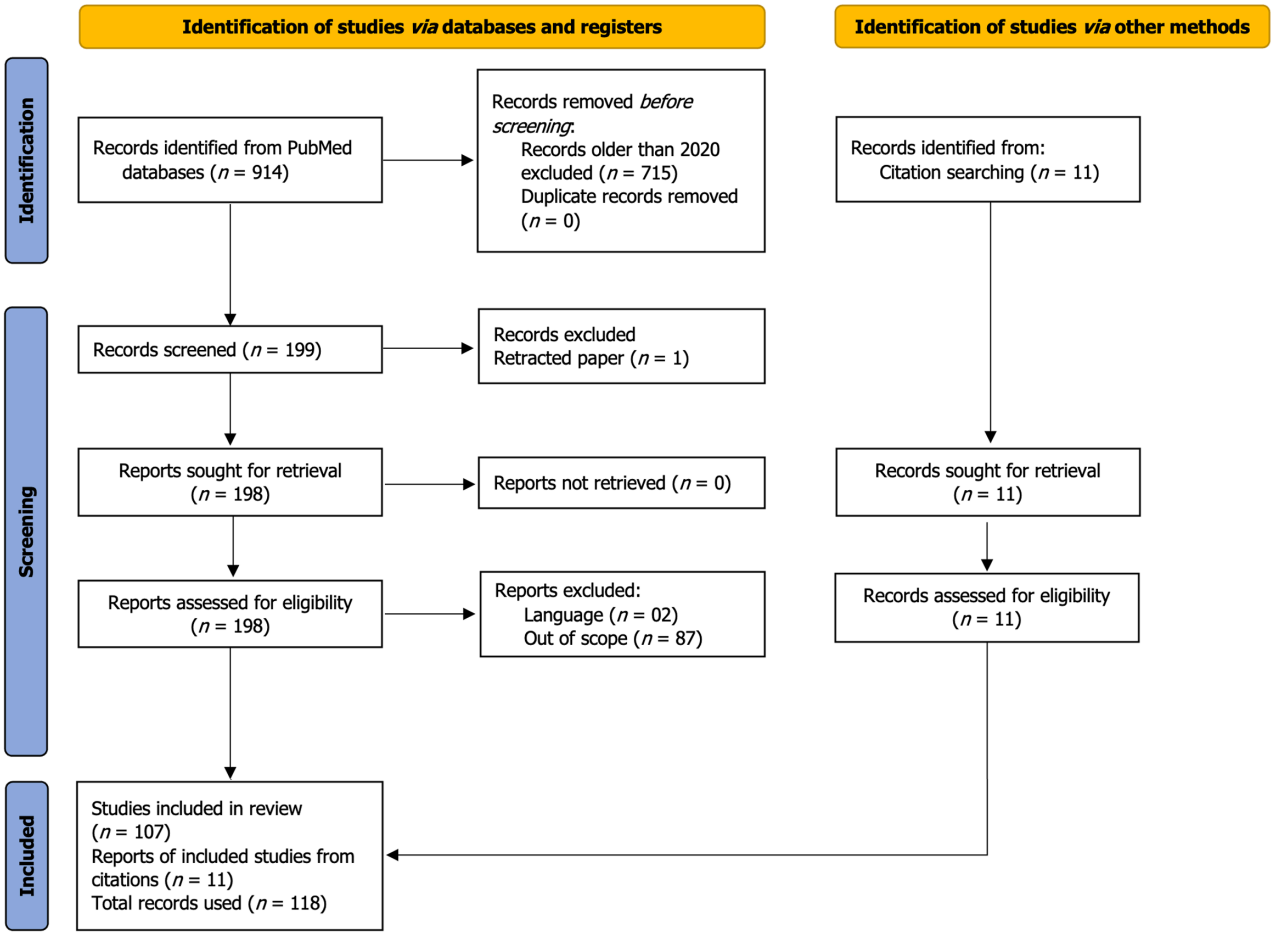


Figure 1 PRISMA guideline showing retrieved records stratification.

Ocular surface disease index

The ocular surface disease index (OSDI) is a questionnaire designed to measure the severity of dry eye symptoms and their impact on daily activities. It covers three main areas: Environmental triggers, visual function, and ocular symptoms [63]. The questionnaire consists of twelve questions, each scored from 0 to 4, with higher scores indicating more severe symptoms[64]. The total OSDI score ranges from 0 to 100 and helps track symptom progression and treatment effectiveness[65]. Table 3 below provides more comprehensive information on the OSDI questionnaire[63-65].

Standard patient evaluation of eye dryness

The standard patient evaluation of eye dryness (SPEED) questionnaire, developed by Korb and Blackie, is a tool used to quickly assess and track the symptoms of DED. It consists of eight questions evaluating the frequency and severity of symptoms such as dryness, grittiness, soreness, irritation, burning, watering, and eye fatigue[66]. Patients rate their symptoms on a scale from 0 to 4, with a total score ranging from 0 to 28. This standardized method helps healthcare providers monitor symptom progression and identify triggers, making it easier to diagnose and manage DED[67]. Its simplicity and efficiency make it useful in both clinical settings and research studies. Table 4 below provides more comprehensive information on the SPEED questionnaire[66,67].

McMonnies dry eye questionnaire

The McMonnies questionnaire is a diagnostic tool used to evaluate the severity and frequency of dry eye symptoms and identify risk factors[68]. It asks about environmental triggers and systemic conditions to help clinicians understand the underlying causes. Higher total scores indicate a greater likelihood of DED, aiding in diagnosis and treatment planning, which may include artificial tears, lifestyle changes, or other therapies to improve the patient's quality of life[69]. Table 5 below provides more comprehensive information on the McMonnies questionnaire[68,69].

Subjective assessments are essential in diagnosing DED, although they require supplementation with objective metrics for precision. The OSDI and SPEED questionnaires offer symptomatic insights but should not serve as the exclusive diagnostic criterion. The OSDI and SPEED questionnaires are mostly diagnostic, evaluating symptom load. The McMonnies questionnaire is primarily designed for screening, but the DryEyeRhythm app facilitates the longitudinal tracking of symptoms. Clinicians must choose instruments according to the specific therapeutic purpose.

Table 3 Ocular surface disease index questionnaire and scoring system[1]

Category	Questions	Scoring (0-4)
Ocular symptoms	Dryness, grittiness, discomfort	0 (None) to 4 (Severe)
Visual function	Blurred vision, difficulty reading	0 (None) to 4 (Severe)
Environmental factors	Wind sensitivity, air conditioning	0 (None) to 4 (Severe)

[1]The ocular surface disease index score is calculated as: Total score = (Sum of responses) × 25/number of questions answered, giving a 0-100 range.

Table 4 Standard patient evaluation of eye dryness questionnaire[1]

Question type	Symptoms evaluated	Scoring (0-4)
Frequency	Burning, grittiness, fatigue	0 (Never) to 4 (Constant)
Severity	Discomfort level	0 (None) to 4 (Severe)

[1]The total standard patient evaluation of eye dryness score (0-28) provides a measure of symptom burden, aiding in dry eye disease diagnosis.

Table 5 McMonnies questionnaire[1]

Question type	Symptoms evaluated	Scoring (0-4)
Risk factors	Age, sex, contact lens use, medications, systemic diseases (*e.g.*, Sjögren's)	Yes/No responses (Binary)
Symptoms frequency	Dryness, grittiness, burning, excessive tearing	0 (Never) to 3 (Frequent)
Symptom severity	Eye discomfort, irritation, redness	0 (None) to 3 (Severe)
Triggers	Environmental factors (wind, air condition, smoke), screen time impact	Yes/No responses (Binary)

[1]The total McMonnies score (0-45) helps assess dry eye disease severity, with higher scores (≥ 14) indicating significant dry eye disease.

Objective measures-tear film stability, ocular surface integrity, and tear production

Proteomic indicators and exosomal biomarkers are recent means of objectively assessing tear film stability in dry eye treatment[70,71]. Although there are many high-end means of objectively assessing individuals with dry eyes, with each method having a specific level of specificity and sensitivity, the gold standard still remains the tear film ocular surface algorithm[72].

In the future, a workup on the particular microbes present in the anterior segment will help control inflammation and ocular surface complications from DED[73].

Tear break-up time, which evaluates tear film stability

Tear break-up time (TBUT) assesses tear film stability by the application of fluorescein dye. A TBUT of less than 10 seconds indicates tear instability. The flowchart image below in Figure 3 illustrates the steps in measuring TBUT. Following a case-control study carried out by Pu *et al*[74], it was observed that assessing first non-invasive TBUT, average non-invasive TBUT, tear meniscus height, and meibomian gland assessment showed a correlation between the onset of obstructive sleep apnea and the onset of DED[74-76]. Ocular surface temperature reduces following phacoemulsification cataract surgery, partly due to instability of the tear film[77], potentially disrupting the tear film (Figure 3).

Fluorescein, rose bengal, and lissamine green staining, which assess ocular surface damage and inflammation

Ocular staining scores evaluate corneal damage utilizing fluorescein or lissamine green dyes, with grading determined by staining intensity. Ocular staining score has been found to have a higher degree of sensitivity and specificity when compared to other dry eye diagnostic parameters[78]. Sahlu *et al*[79] conducted a cross-sectional study and observed a significant drop in TBUT and corneal staining in glaucoma patients, especially those on multiple drops[79,80].

Using parameters like the Schirmer test score, Corneal staining score, and worse composite DED sign score as criteria for gender prevalence of complaints and in premenopausal and post-menopausal women, the result was in favor of premenopausal women compared to those that have reached menopause[81]. Software assessment of corneal staining, compared to individual objective assessment, shows more accuracy and is deemed fit to be used for monitoring purposes [82-84].

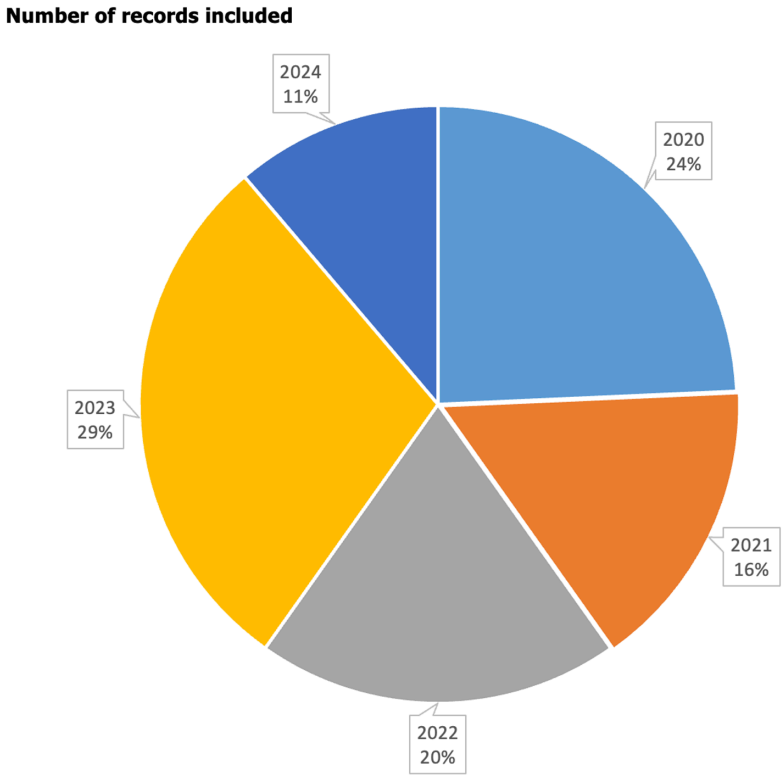


Figure 2 Distribution of records used by year.

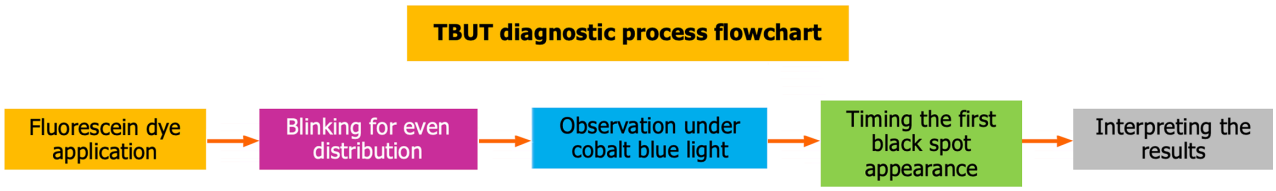


Figure 3 Tear break-up time diagnostic flowchart. TUBT: Tear break-up time.

Tear osmolarity measurement, indicative of tear film quality

It was found in the DREAM study that there is no significant relationship between tear osmolarity in a patient with dry eyes and DED symptoms, so changes in tear film osmolarity cannot be regarded as a causal factor for the development or worsening of dry eyes[85,86]. A controlled environment chamber technique can be used in the assessment of dry eye complaints and symptoms, as it allows researchers to manipulate the testing location while observing tear parameters [87]. The OcuSense TearLab osmometer is a digital device that measures tear osmolarity from a very small sample. García *et al*[88]showed that this osmometer had good reproducibility indices and as such, can be very handy in DED diagnosis.

Tear volume assessment via Schirmer's test, evaluating tear production

The Schirmer's test evaluates tear volume using a wettable strip inserted into the lower fornix. Tortuous meibomian gland and a high composite score for features of the meibomian gland was associated with longer TBUT and longer length on the Schirmer strip[89]. The Schirmer test is the most common test for tear quantity and it is a tool for verifying/standardizing other tear volume testing techniques[90,91].

In cases of aqueous-deficient DED, Schirmer's test and tear osmolarity assessments are the most pertinent. In evaporative DED, meibography and lipid layer thickness assessment are essential. The prognostic evaluation is enhanced by OCT-based monitoring of tear meniscus height and *in vivo* confocal microscopy for assessing nerve injury.

Advanced imaging techniques

In vivo, confocal microscopy is a great tool for assessing neurosensory changes that occur in eyes with DED[92]. These imaging techniques in DED management are more objective and provide real-time documentation of parameters both now and in the near future[93]. There is an emergence in the use of protein microarray technology in the management of ocular surface disease caused or worsened by diabetes[94]. Tracking field failure has been found to increase the severity of dry eyes, suggesting that the reduced lubrication occasioned by DED affected eye movement[95,96]. The use of app-based software in diagnosing dry eyes is, however, gaining more ground and has been found to offer as much

information as the traditional diagnostic technique[97].

Optical coherence tomography

Epithelial thickness profile range and Epithelial irregularity factor obtained by using ultra-high OCT have been found to correlate with patient's complaints and symptoms, viz a viz, there is a direct relationship between symptoms and these two parameters[98]. There seems to be a significant difference in corneal morphology parameters when using Pentacam and the anterior segment OCT as measuring tools[99]. The most reliable method of assessing the tear meniscus height is the use of OCT, followed by the regular slit lamp examination. However, comparing tear meniscus height with lid margin thickness or number of lashes is not a reliable method as shown by research work[100].

The DryEyeRhythm app, an innovative tool developed by Juntendo University, serves as a sophisticated mechanism for the monitoring and management of dry eye symptoms. Utilizing the smartphone's camera for conducting a blink assessment, coupled with a concise questionnaire, users are afforded the capability to determine their dry eye score within a brief duration of approximately five minutes[52]. The application further enables users to systematically track daily lifestyle variables, including stress levels and sleep patterns, thereby elucidating the relationship between these factors and dry eye symptoms. The anonymized data collected *via* the app significantly contributes to dry eye research, facilitating advancements in early detection and treatment strategies[84].

Color Doppler imaging (CDI) has emerged as a valuable diagnostic tool in the assessment of ocular blood flow abnormalities associated with DED. By employing this non-invasive ultrasound technique, clinicians can visualize and quantify blood flow in the ophthalmic vessels, including the central retinal artery and posterior ciliary arteries[53]. CDI facilitates the detection of hemodynamic changes that may contribute to the pathophysiology of dry eye, such as reduced blood flow velocity and altered resistivity indices[53]. This advanced imaging modality offers a promising approach for early diagnosis and monitoring of DED, potentially leading to more effective therapeutic interventions and improved patient outcomes

Meibography

Meibography employs infrared imaging to visualize the morphology of meibomian glands. Atrophy and gland loss correspond with the severity of DED. With this technique, the lower lid is everted and imaged. The image generated is then assessed and graded to account for any dilation, or atrophy blockage in the meibomian glands. This technique offers detailed anatomical insights into meibomian glands, aiding in diagnosing underlying structural abnormalities[101]. By capturing detailed images, meibography helps identify blockages or atrophy in these glands, which are essential for producing the lipid layer of the tear film that prevents tear evaporation. When combined with other dry eye tests, such as TBUT, osmolarity tests, and questionnaires like the OSDI, meibography provides a comprehensive understanding of a patient’s dry eye condition[102]. The use of the noninvasive keratograph, tear meniscus height, and bulbar injection, when compared to other clinical evaluation techniques such as the Schirmer test, *etc.*, showed no correlation between the two techniques using the ocular surface disorder score[103]. In the detection of underlying issues, it has been found that there is a correlation between the onset of anterior segment endothelial anomalies in patients with dry eye.

Matrix metalloproteinase-9 testing

Inflammatory biomarkers testing provide additional diagnostic precision, particularly in identifying inflammatory components of DED[104,105]. The ability to assess matrix metalloproteinase-9 can be a helpful tool in measuring response to treatment and monitoring the course of disease in cases of dry anophthalmic socket syndrome[104]. It was found that both patients with DED without Sjogren disease and those with Sjogren disease, with positive metalloproteinase-9, showed lower tear secretion and high tear osmolarity compared to those with negative metalloproteinase-9[106].

Artificial intelligence and DED diagnosis

Artificial intelligence (AI) algorithms evaluate ocular images to identify early biomarkers of DED, improving diagnostic precision and efficiency. Deep learning algorithms, particularly deep transfer learning is said to be a new way of automatically analyzing inflammatory markers in the diagnosis and management of DED[107]. As an example, machine learning models have been shown to identify an increase or upregulation of tear proteins, in cases of DED of Sjogren origin or KCS [108,109]. These advancements in DED diagnostics enables better sensitivity in comparison to traditional methods.

Besides the use of AI in tear protein analysis as discussed earlier, it has also been integrated into immunoassay-based diagnostic techniques like the Chemiluminescent immunoassay and the Siemens immunonephelometric assay, which are close to precise methods for detecting immunoglobulins in related diseases and PSS[110]. There is an increased demand for the standardization of Schirmer’s strip production, processing of tear fluid, and analyte concentration normalization, and AI is primed to step in to ensure consistency and reproducibility in diagnostic protocols[111].

In addition to these efforts, AI models also support in clinical decision-making to assist eye care practitioners in the diagnosis of DED. For instance, Chatzaki *et al*[112] successfully developed an electronic tool for training primary eye care providers on accurate diagnosis of DED with commendable success with a 97.2% reported usability score[112].

To guarantee a methodical approach in diagnosing DED, the subsequent sequence is advised

Symptom evaluation: Employ validated questionnaires like the OSDI or SPEED to ascertain the intensity and frequency of symptoms.

Assess tear film stability: Perform TBUT and measure tear osmolarity to determine tear film integrity.

Ocular surface staining: Employ fluorescein and lissamine green staining to identify corneal injury.

Tear volume assessments: Conduct Schirmer's test to evaluate tear production.

Imaging techniques: Meibography for assessing meibomian gland functionality and OCT for measuring tear meniscus.

Confirmatory and prognostic assessment: Employ *in vivo* confocal microscopy for nerve examination and tear film proteomics for inflammatory biomarkers.

Management strategies, comparison of treatment plan: Current and future frontiers

DED therapy includes artificial tears, anti-inflammatory medications, punctal occlusion, and lifestyle adjustments. Recent therapeutics encompass regenerative medicine and biologics. Approved treatments encompass artificial tears, cyclosporine A, lifitegrast, and punctal plugs. Innovative therapies like regenerative eye drops and mesenchymal stem cell treatment are still in the experimental phase. Recent trials indicate that biologic medicines aimed at inflammation (*e.g.*, IL-1 inhibitors) may surpass traditional anti-inflammatories in severe DED.

In the use of artificial tears as a DED therapy, the use of ocular lubricant for individuals with reflex tearing usually improves their complaints[113]. However, the use of orthokeratology lenses has been found to have little or no effect on tear film stability[114].

The addition of tear supplements to steroid and non-steroidal anti-inflammatory drugs following cataract surgery has been found to lessen DED symptoms post-operatively[115-117]. Water-free topical cyclosporin 0.1%, when used in comparison to a vehicle, had an earlier therapeutic effect on the ocular surface[118-120]. Hydroxyquinoline, when combined with cyclosporine, improved the Schirmer score and significantly reduced surface inflammation[121]. Topical spironolactone helps in the production of the lipid layer of tear film, which helps to reduce surface inflammation in cases of graft *vs* host disease[122]. Placebos have been employed to measure the intervention's efficacy in treating dry eyes[123].

Treating dry eyes with hyaluronic acid and Ginkobiloba eye drops significantly improves the symptoms of DED[124]. There is, however, no significant difference in the prolonged use of omega-3 fatty acids compared with those who discontinued their usage at some point[125-127]. Research has shown that Lacrimera drops improve dry eye treatment, using TBUT, Schirmer analysis, and corneal staining as parameters, and it has been found to have a high-level regeneration time that can be sustained for about a month after use[128]. Semi-fluorinated alkane eye drops improve symptoms of dry eyes in patients who underwent cataract surgery[129]. A similar outcome was achieved when a mirrored demographic was treated with sodium hyaluronate and dexpanthenol-containing eye drops also after cataract extraction[130].

Current studies on recombinant growth factors have been shown to give good symptom relief in the treatment of dry eyes[131]. The management of conjunctivochalasis is an important antidote in managing patients with dry eyes, especially those using high-frequency radio wave electrosurgery[132]. The use of contact lenses has been found to reduce inflammatory cell numbers on the ocular surface, thereby presenting a possible future management strategy for dry eyes [133] as it enhanced corneal nerve health while reducing activated/mature corneal inflammatory cell numbers, delivering a safe and promising new treatment for moderate-to-severe DED. Loteprenol-tobramycin combination drops have shown some promise in mitigating DED symptoms and progression, lending a voice to the characterization of DED and the inflammatory process[134].

In studies by Moon *et al*[135], autologous epithelial growth factor ointment successfully reduced areas of epithelial damage. Punctual cauterization using heat treatment can be helpful when dealing with severe, potentially scarring dry eyes[136]. In a similar vein, mesenchymal stem cells show promise in managing Sjorgen syndrome[137,138] due to their ability to stimulate nuclear factor id3. A summary of some of the methods used to manage dry eyes is shown in Table 6.

Post coronavirus disease 2019 considerations in DED diagnosis and management

The SARS-CoV-2 virus has forever changed the face of medicine and healthcare as we knew it[139-141]. In China and Italy for example, research has shown that the coronavirus disease 2019 (COVID-19) exacerbated symptoms in patients with rheumatoid related conditions, which are in themselves linked to DED[140-143]. The IMPULSE study carried out in Spain recommended that tele-healthcare can be utlized to mitigate DED-linked ocular morbidity[144]. Brito-Zerón *et al* [145] also reported a positive correlation between DED and exacerbation of COVID linked morbidities.

This paper was limited to reviewing records in the search pool published not older than 2020. A wider search criterion may have yielded more data to sample.

CONCLUSION

In conclusion, the effective management of DED begins with an accurate diagnosis. Integrating a combination of subjective and objective diagnostic tools allows clinicians to comprehensively assess the condition, tailor treatment plans, and monitor therapeutic efficacy. Continued advancements in diagnostic technologies promise to enhance our understanding and management of this prevalent ocular condition.

Table 6 Management of dry eyes

Category	Ref.	Management tool	Details description
Management strategies	Akpek *et al*[118]	Topical cyclosporine 0.1%	A water-free cyclosporine formulation that improves the ocular surface in moderate-to-severe dry eye
	Fogagnolo *et al* [124]	Hyaluronic acid and ginkgo biloba drops	Effective in improving symptoms, especially post-cataract surgery
	Wirta *et al*[131]	Recombinant human nerve growth factor	Promising in treating moderate-to-severe dry eye by enhancing corneal nerve regeneration
	Hu *et al*[138]	Mesenchymal stem cells	Shows promise in managing Sjögren's syndrome, potentially aiding in ocular surface repair
Surgical options	Wang *et al*[136]	Punctal cauterization	Heat treatment that is useful for severe dry eye, particularly in preventing scarring
	Ji *et al*[139]	High-frequency radiowave electrosurgery	Improves conjunctivochalasis, reducing symptoms and improving management outcomes
Post-COVID-19 Considerations	Castillo *et al* [144]	Telehealthcare	Utilized to mitigate DED-linked ocular morbidity, particularly relevant post-COVID-19

DED: Dry eye disease; COVID-19: Coronavirus disease 2019.

FOOTNOTES

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SYSTEMATIC REVIEWS

Accuracy of artificial intelligence in meta-analysis: A comparative study of ChatGPT 4.0 and traditional methods in data synthesis

Aman Goyal, Muhammad Daoud Tariq, Areeba Ahsan, Muhammad Hamza Khan, Amna Zaheer, Hritvik Jain, Surabhi Maheshwari, Andrei Brateanu

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Abstract

BACKGROUND

Meta-analysis is a critical tool in evidence-based medicine, particularly in cardiology, where it synthesizes data from multiple studies to inform clinical decisions. This study explored the potential of using ChatGPT to streamline and enhance the meta-analysis process.

AIM

To investigate the potential of ChatGPT to conduct meta-analyses in interventional cardiology by comparing the results of ChatGPT-generated analyses with those of randomly selected, human-conducted meta-analyses on the same topic.

METHODS
We systematically searched PubMed for meta-analyses on interventional cardiology published in 2024. Five meta-analyses were randomly chosen. ChatGPT 4.0 was used to perform meta-analyses on the extracted data. We compared the results from ChatGPT with the original meta-analyses, focusing on key effect sizes, such as risk ratios (RR), hazard ratios, and odds ratios, along with their confidence intervals (CI) and *P* values.

RESULTS
The ChatGPT results showed high concordance with those of the original meta-analyses. For most outcomes, the effect measures and *P* values generated by ChatGPT closely matched those of the original studies, except for the RR of stent thrombosis in the Sreenivasan *et al* study, where ChatGPT reported a non-significant effect size, while the original study found it to be statistically significant. While minor discrepancies were observed in specific CI and *P* values, these differences did not alter the overall conclusions drawn from the analyses.

CONCLUSION
Our findings suggest the potential of ChatGPT in conducting meta-analyses in interventional cardiology. However, further research is needed to address the limitations of transparency and potential data quality issues, ensuring that AI-generated analyses are robust and trustworthy for clinical decision-making.

Key Words: ChatGPT; Artificial intelligence; Large language model; Meta-analysis; Statistical analysis; Methodology; Cardiology

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Core Tip: This study explored the potential of using ChatGPT 4.0 to conduct meta-analyses. Five meta-analyses were systematically selected. ChatGPT 4.0 was used to perform meta-analyses on the extracted data, and the results were compared with the original meta-analyses. The results generated by ChatGPT 4.0 showed high concordance with those of the original meta-analyses. For most outcomes, the effect measures and p-values generated by ChatGPT 4.0 closely matched those of the original studies. Our findings suggest the potential of ChatGPT 4.0 in conducting meta-analyses in cardiology.

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INTRODUCTION

Meta-analysis is a powerful tool in evidence-based medicine that provides a systematic approach for synthesizing data from multiple studies to derive conclusions about medical interventions. In interventional cardiology, where new technologies and procedures are constantly emerging, meta-analysis plays a vital role in evaluating their effectiveness and safety compared to existing methods. This information is crucial for informing clinical guidelines and practices[1]. The rigorous process of conducting a meta-analysis involves comprehensive literature searches, data extraction, statistical analysis, and critical interpretation, which often requires substantial expertise and time[2]. However, the advent of artificial intelligence (AI) technologies, such as ChatGPT developed by OpenAI, offers new opportunities to streamline and potentially expedite this process.

ChatGPT is an AI language model that uses machine learning techniques to generate human-like text based on the input it receives. It is trained on a vast text corpus, allowing it to understand and respond to various topics, including medical research[3]. Recent studies have shown that AI can effectively assist in various aspects of medical research[4]. For instance, AI has been used to automate the screening of abstracts and full-text articles during the systematic review process, thereby significantly reducing the time required for these tasks[5]. Moreover, AI-driven tools have demonstrated high accuracy in identifying relevant studies and extracting key data points, which are critical steps in conducting meta-analyses[6].

Despite these promising developments, the application of AI in meta-analyses remains in its early stages and there are several challenges to address. One of the primary concerns is the transparency and interpretability of AI-generated results. Although AI models such as ChatGPT can produce coherent and relevant text, the underlying decision-making process is often a "black box," making it difficult for researchers to understand how conclusions are derived[7]. Ensuring that AI-generated analyses are transparent and can be validated by human experts is essential for their acceptance and use in clinical research[8]. Another challenge is the need for high-quality curated datasets to train the AI models. The reliability of AI-generated analyses depends on the quality of the input data, and any bias or error in the training data can affect the outcome[9]. Therefore, ongoing efforts to improve the data quality and develop robust training datasets are crucial for advancing the use of AI in meta-analyses.

This study investigated the potential of ChatGPT to conduct meta-analyses in interventional cardiology by comparing the results of ChatGPT-generated analyses with those of randomly selected, human-conducted meta-analyses on the same topic. By identifying potential discrepancies and insights, this study aimed to evaluate the reliability and utility of ChatGPT as a tool for supporting meta-analyses in this field.

MATERIALS AND METHODS

Search strategy and eligibility criteria

PubMed was systematically searched using the following search strategy: (interventional cardiology) OR (cardiac intervention) OR (catheterization) OR (cardiology) OR (cardiac catheterization) AND (angioplasty) OR (stenting) OR (percutaneous coronary intervention) OR (valvuloplasty) OR (transcatheter aortic valve replacement)) OR (TAVR) OR (angioplasty, balloon) OR (atherectomy, coronary) OR (valvuloplasty) AND (coronary artery disease) OR (myocardial infarction)) OR (ischemic heart disease)) OR (structural heart disease)) OR (congenital heart disease) OR (heart defects, congenital) AND (meta-analysis) OR (meta-analysis).

Two independent reviewers screened the retrieved titles and abstracts according to pre-established eligibility criteria, focusing on studies involving adult patients undergoing interventional cardiology procedures, investigating procedural effects or techniques, and reporting relevant clinical outcomes such as mortality, major adverse cardiovascular events (MACE), stent thrombosis, and revascularization rates. Only studies identified as meta-analyses that were published in peer-reviewed journals in 2024 were considered. Observational studies, randomized controlled trials, network meta-analyses, reviews, and articles that were not available in English were excluded.

Study selection

We chose five meta-analyses in our study because we believe this number provides a well-balanced mixture of different effect measures, software utilized by the included studies, and journals, offering a thorough insight into the capabilities of ChatGPT in statistical analyses. Five meta-analyses were randomly selected from the final list of eligible studies using a random number generator to minimize selection bias. Random selection ensured that each eligible study had an equal chance of being included, thereby avoiding subjective bias in article selection.

Data extraction from meta-analyses

Two independent reviewers (Tariq MD, Ahsan A) extracted quantitative data (events/total or events/non-events in the interventional and control groups) from each selected meta-analysis using a predefined data extraction sheet. Extracted data included study ID, journal in which the study was published, outcome measures, type of effect measure, and the effect measure value and p-value reported by the meta-analysis and generated by ChatGPT.

Data analysis by ChatGPT

The quantitative data extracted from the meta-analyses were inputted into ChatGPT 4.0 for analysis generation. ChatGPT was used to perform a meta-analysis to calculate the pooled effect measures [risk ratio (RR), hazard ratio (HR), and odds ratio (OR)] along with their corresponding 95% confidence intervals (CIs) and *P* values. The ChatGPT was instructed to utilize either a fixed-effects or random-effects model based on the specific approach employed in the original meta-analysis for consistency. The results generated by the ChatGPT were compared with the analysis results from each meta-analysis to identify any significant discrepancies. The prompts given to ChatGPT and the corresponding generated results are provided in the Supplementary material.

RESULTS

The initial search yielded a total of 135 results. Of these, five studies were randomly selected for inclusion in the comparative analysis[10-14]. All outcomes reported in each study were analyzed and compared with the results obtained using the ChatGPT. The included studies were published in the following journals: *Journal of the American Heart Association*[10], *Circulation*[11], *American Journal of Cardiology*[12], *European Heart Journal*[13], and *International Journal of Cardiology*[14]. The reported effect measures included RR, HR, and OR with their corresponding 95%CI and *P* values. A comparison of the effect measures and p-values between the original studies and the ChatGPT is summarized in Table 1. The comparison between the two groups for various outcome measures, including effect sizes and their 95%CIs, is depicted using bar graphs in Figure 1.

Study 1

Major adverse cardiovascular events: The RR calculated by ChatGPT (0.67, 95%CI: 0.56-0.81) was very close to the original (0.67, 95%CI: 0.55-0.82)[10], demonstrating high concordance. Both analyses indicated a statistically significant reduction in MACE, with *P*-values in agreement ($P < 0.001$ for both ChatGPT and the original).

Cardiac death: ChatGPT provided an RR of 0.46 (95%CI: 0.29-0.72) compared to the original 0.49 (95%CI: 0.34-0.71)[10]. Both analyses showed a significant reduction in cardiac death, with $P < 0.001$ for both.

Table 1 Comparison of effect measures and *P* values between original studies and ChatGPT

Ref.	Journal	Software used for analysis	Outcome measures	Type of effect measure	Effect measure (original)	*P* value (original)	Effect measure (ChatGPT)	*P* value (ChatGPT)
Sreenivasan *et al*[10]	*Journal of American Heart Association*	R studio	MACE	Risk ratio (95%CI)	0.67 (0.55 - 0.82)	< 0.001	0.67 (0.56-0.81)	< 0.001
			Cardiac death	Risk ratio (95%CI)	0.49 (0.34 - 0.71)	< 0.001	0.46 (0.29-0.72)	< 0.001
			All-cause death	Risk ratio (95%CI)	0.81 (0.61 - 1.07)	0.135	0.80 (0.60-1.06)	0.124
			Myocardial infarction	Risk ratio (95%CI)	0.82 (0.62-1.07)	0.144	0.84 (0.64-1.10)	0.197
			Target vessel MI	Risk ratio (95%CI)	0.61 (0.42-0.89)	0.011	0.61 (0.42-0.90)	0.011
			Target lesion revascularization	Risk ratio (95%CI)	0.67 (0.49-0.91)	0.011	0.66 (0.48-0.91)	0.010
			Target vessel revascularization	Risk ratio (95%CI)	0.60 (0.45-0.80)	< 0.001	0.60 (0.45-0.80)	< 0.001
			Stent thrombosis	Risk ratio (95%CI)	0.63 (0.40-0.99)	0.046	0.67 (0.42-1.06)	0.090
Patel *et al*[11]	Circulation	R studio	MACE	Hazard ratio (95%CI)	0.91 (0.87-0.96)	< 0.0001	0.94 (0.90-0.98)	0.005
			Cardiovascular death	Hazard ratio (95%CI)	0.86 (0.81-0.92)	< 0.0001	0.88 (0.81-0.96)	0.0037
			Myocardial infarction	Hazard ratio (95%CI)	0.95 (0.87-1.04)	0.29	0.97 (0.90-1.05)	0.429
			Stroke	Hazard ratio (95%CI)	0.99 (0.91-1.07)	0.77	0.87 (0.65-1.18)	0.380
Sacoransky *et al*[12]	*American Journal of Cardiology*	RevMan	LV thrombus formation	Odds ratio (95%CI)	0.28 (0.11-0.73)	< 0.01	0.37 (0.16-0.86)	0.021
			Major bleeding events	Odds ratio (95%CI)	2.85 (1.13-7.24)	0.03	2.82 (1.30-6.13)	0.009
			Systemic embolism	Odds ratio (95%CI)	0.37 (0.12-1.13)	0.08	0.42 (0.13-1.29)	0.130
Paolucci *et al* [13]	*European Heart Journal*	RevMan	Relationship between PMI (UDMI and UDMI-like definitions) and mortality	Hazard ratio (95%CI)	1.61(1.32-1.97)	< 0.00001	1.61 (1.32-1.97)	< 0.00001
			Relationship between PMI (ARC-2 definition) and mortality	Hazard ratio (95%CI)	2.07 (1.40-3.08)	0.0003	2.07 (1.40-3.08)	0.0003
			Relationship between PMI (SCAI and SCAI-like definitions) and mortality	Hazard ratio (95%CI)	3.24 (2.36-4.44)	< 0.00001	3.24 (2.36-4.44)	< 0.00001
Ang *et al*[14]	*International Journal of Surgery*	Stata	Major vascular complications	Risk ratio (95%CI)	2.32 (1.73-3.11)	< 0.001	2.30 (1.72-3.09)	< 0.001
			Major bleeding	Risk ratio (95%CI)	1.61 (1.27-2.05)	< 0.001	1.61 (1.27-2.05)	< 0.001
			Aortic annulus rupture	Risk ratio (95%CI)	4.66 (1.67-13.01)	< 0.001	4.66 (1.67-13.01)	0.0033
			Cardiac tamponade	Risk ratio (95%CI)	3.0 (1.31-6.89)	0.01	3.0 (1.31-6.89)	0.0095
			Minor vascular complications	Risk ratio (95%CI)	1.43 (1.00-2.04)	0.05	1.43 (1.00-2.04)	0.052
			Stroke	Risk ratio (95%CI)	1.37 (0.81-2.32)	0.24	1.41 (0.82-2.40)	0.210
			In-hospital mortality	Risk ratio	1.86 (0.74-	0.19	1.86 (0.74-4.70)	0.187

		(95%CI)	4.70)		
	30 days mortality	Risk ratio (95%CI)	1.14 (0.532.46)	0.74	1.22 (0.55-2.71) 0.628
	Pacemaker implantation	Risk ratio (95%CI)	0.91 (0.70-1.18)	0.47	0.98 (0.75-1.26) 0.848

MACE: Major adverse cardiac events; MI: Myocardial infarction; LV: Left ventricular.

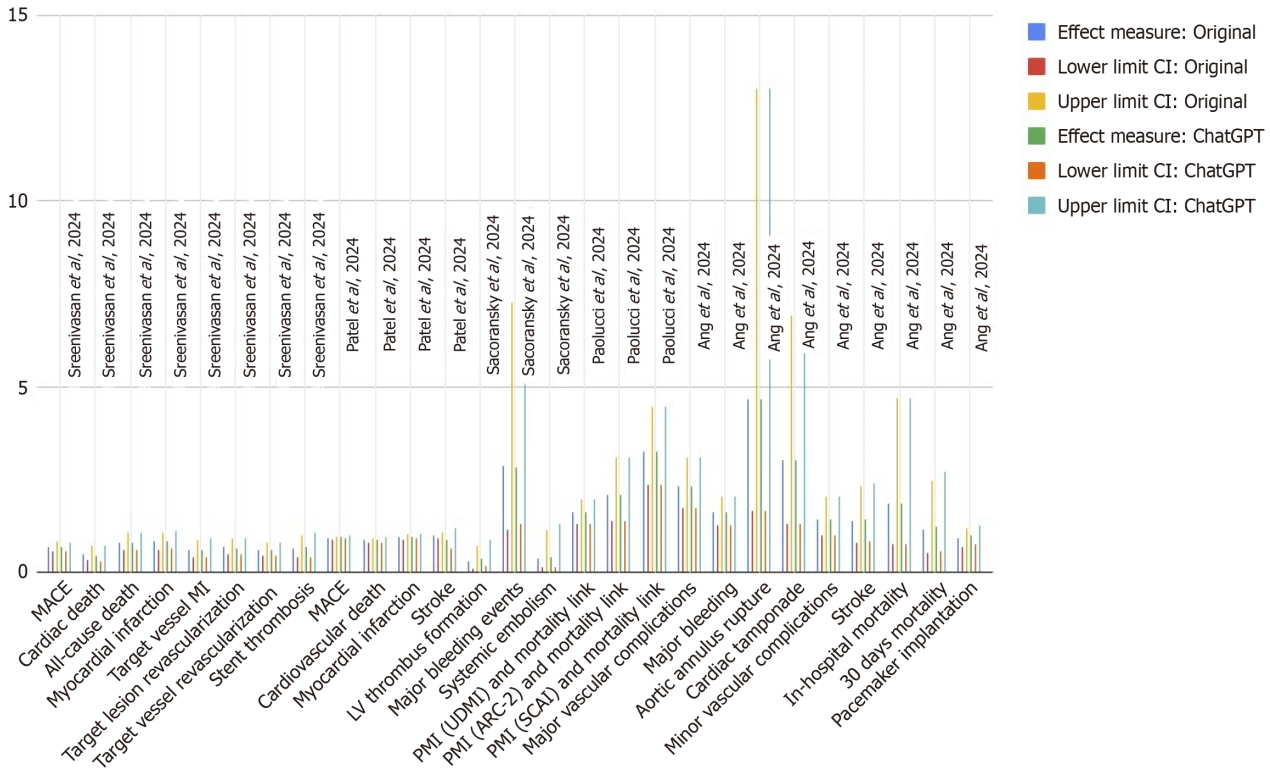


Figure 1 Comparison between the traditional and ChatGPT models for various outcome measures, including effect sizes and their 95% confidence interval.

All-cause death: The RR for ChatGPT (0.80, 95%CI: 0.60-1.06) was comparable to the original (0.81, 95%CI: 0.61-1.07)[10]. Neither analysis showed a statistically significant reduction in all-cause mortality (P = 0.124 for ChatGPT and 0.135 for original), suggesting close agreement.

Myocardial infarction: Both analyses yielded similar insignificant RRs, with ChatGPT reporting 0.84 (95%CI: 0.64-1.10) and the original 0.82 (95%CI: 0.62-1.07)[10]. In this case, the P value from the original analysis (0.144 *vs* 0.197) is slightly lower.

Target vessel myocardial infarction: The RR of ChatGPT (0.61, 95%CI: 0.42-0.90) was consistent with the original RR (0.61, 95%CI: 0.42-0.89)[10], with P values (0.011 *vs* 0.011) indicating statistical significance with agreement in both analyses.

Target lesion revascularization: The RR from both analyses were similar (ChatGPT: 0.66, 95%CI: 0.48-0.91; original: 0.67, 95%CI: 0.49-0.91)[10], with ChatGPT's P-value (0.010), suggesting high concordance with the original P value (0.011).

Target vessel revascularization: Both analyses reported the same RR and CI (0.60, 95%CI: 0.45-0.83), with similar P values (< 0.001).

Stent thrombosis: ChatGPT reported an RR of 0.67 (95%CI: 0.42-1.06) compared to the original 0.63 (95%CI: 0.40-0.99)[10]. The P value from ChatGPT (0.090) indicated non-significance, whereas the original P value (0.046) suggested significance, highlighting a notable difference in the interpretation. Variations in the statistical methods used by ChatGPT and the original analysis could have influenced the P value.

Study 2

MACE: ChatGPT's HR (0.94, 95%CI: 0.90-0.98) was slightly higher than the original (0.91, 95%CI: 0.87-0.96)[11], with both analyses indicating a significant risk reduction. Although ChatGPT's *P* value (0.005) was close to the original (*P* < 0.0001), the original demonstrated a greater statistical significance.

Cardiovascular death: The HR was similar (ChatGPT: 0.88, 95%CI: 0.81-0.96; original: 0.86, 95%CI: 0.81-0.92)[11], with both analyses showing significant risk reduction. However, the original *P* value (< 0.0001) indicated a greater level of statistical significance than ChatGPT's *P* value (0.0037).

Myocardial infarction: ChatGPT HR (0.97, 95%CI: 0.90-1.05) showed no significant risk reduction, similar to the original (0.95, 95%CI: 0.87-1.04)[11]. However, the ChatGPT *P* value (0.429) was greater than the original value (0.29), reflecting variations in the statistical interpretation.

Stroke: ChatGPT reported an HR of 0.87 (95%CI: 0.65-1.18) compared to the original 0.99 (95%CI: 0.91-1.07)[11]. However, both *P* values (ChatGPT: 0.380, original: 0.77) indicated a lack of statistical significance, with slight differences in the HR estimates.

Study 3

LV thrombus formation: The ORs were nearly similar (ChatGPT: 0.37, 95%CI: 0.16-0.86; original: 0.28, 95%CI: 0.11-0.73)[12], with both analyses showing a significant reduction; however, ChatGPT's *P* value (0.021) was slightly greater than the original (< 0.01).

Major bleeding events: The OR of 2.82 using ChatGPT (95%CI: 1.30-6.13) was similar to the original 2.85 (95%CI: 1.13-7.24)[12]. Both *P* values (0.009 ChatGPT *vs* 0.03 original) indicated statistical significance, with greater significance seen in the analysis by ChatGPT.

Systemic embolism: ChatGPT's OR (0.42, 95%CI: 0.13-1.29) was almost similar to the original (0.37, 95%CI: 0.12-1.13)[12], with both analyses showing no significant reduction, although ChatGPT's *P* value (0.130) was greater than the original (0.08).

Study 4

Periprocedural myocardial infarction (UDMI and UDMI-like definitions) and mortality: The HR of ChatGPT (1.61, 95%CI: 1.32-1.97) was similar to the original HR (1.61, 95%CI: 1.32-1.97)[13], with both analyses demonstrating significant associations. In addition, the ChatGPT *P* value (< 0.00001) was consistent with the original (< 0.00001).

Periprocedural myocardial infarction (ARC-2 definition) and mortality: Both the ChatGPT and original analyses reported identical HR (2.07, 95%CI: 1.40-3.08)[13] and *P* values (0.0003), indicating perfect agreement.

Periprocedural myocardial infarction (SCAI and SCAI-like definitions) and mortality: The HR of ChatGPT (3.24, 95%CI: 2.36-4.44) was similar to the original HR (3.24, 95%CI: 2.36-4.44)[13], with both analyses showing significant associations and *P* values in agreement (< 0.00001).

Study 5

Major vascular complications: The RR calculated by ChatGPT was 2.30 (95%CI: 1.72-3.09), closely matching the original study's 2.32 (95%CI: 1.73-3.11)[14]. Both analyses demonstrated a significant reduction in cardiac death, with p-values aligned with each other (*P* < 0.001).

Major bleeding: ChatGPT's calculated RR of 1.61 (95%CI: 1.27-2.05) was similar to the original 1.61 (95%CI: 1.27-2.05)[14], showing high precision. Both analyses indicated a statistically significant reduction in major bleeding events. Both ChatGPT and the original reported *P* values of < 0.001.

Aortic annulus rupture: The RR calculated by ChatGPT (4.66, 95%CI: 1.67-13.01) was similar to the original (4.66, 95%CI: 1.67-13.01)[14]. Both analyses reported a significant reduction in all-cause death, with *P* values of 0.0033 (ChatGPT) and < 0.001 (original), respectively, indicating close agreement.

Cardiac tamponade: ChatGPT reported an RR of 3.0 (95%CI: 1.31-6.89), similar to the original 3.0 (95%CI: 1.31-6.89)[14]. The *P* value from ChatGPT (0.0095) was similar to the original *P* value (0.01) after rounding off ChatGPT's *P* value.

Minor vascular complications: ChatGPT's RR of 1.43 (95%CI: 1.00-2.04) was consistent with the original 1.43 (95%CI: 1.00-2.04)[14]. Similarly, the *P* values (0.052 ChatGPT *vs* 0.05 original) indicated perfect agreement, with statistical significance.

Stroke: The RR was similar, with ChatGPT reporting 1.41 (95%CI: 0.82-2.40) compared to the original 1.37 (95%CI: 0.81-2.32)[14]. The *P* value from ChatGPT (0.210) was nearly identical to the original value (0.24), with neither reaching statistical significance.

In-hospital mortality: ChatGPT's RR of 1.86 (95%CI: 0.74-4.70) was consistent with the original 1.86 (95%CI: 0.74-4.70)[14], and the *P* values (0.187 *vs* 0.19) were insignificant and similar in both groups.

30-days mortality: ChatGPT reported an RR of 1.22 (95%CI: 0.55-2.71) compared to the original 1.14 (95%CI: 0.53-2.46) [14]. The *P* values from ChatGPT (0.628) and the original (0.74) were not significant in either case.

Pacemaker implantation: ChatGPT reported an RR of 0.98 (95%CI: 0.75-1.26) compared to the original 0.91 (95%CI: 0.70-1.18)[14]. The *P* values from the ChatGPT (0.848) and the original (0.47) were not significant in either analysis.

DISCUSSION

Our study aimed to assess the accuracy and reliability of AI-generated meta-analyses by directly comparing the results produced by the ChatGPT with those from traditional meta-analyses in the field of interventional cardiology. Our comparison across various effect sizes (RR, HR, and OR) across a range of outcome measures revealed a remarkable degree of consistency between the results generated by the ChatGPT and the original studies. Both analyses yielded similar effect sizes and corresponding conclusions, with the exception of the RR for stent thrombosis in the Sreenivasan *et al*[10] study. In this specific case, the ChatGPT reported a non-significant effect size, whereas the original study concluded that it was statistically significant. This discrepancy highlights the importance of considering both the effect size and level of statistical significance when interpreting the results. It is important to note that although the effect sizes were similar, there were slight differences in the CIs and *P* values across the analyses. This may be due to chance variations or differences in the analysis methods. More data and larger studies are needed to provide more conclusive evidence.

Interventional cardiology has seen rapid advancements, with numerous studies investigating the efficacy and safety of various interventions such as percutaneous coronary intervention, drug-eluting stents, and novel anticoagulants[10-14]. These studies often produce large volumes of data that must be systematically reviewed and synthesized to guide clinical practice. Traditional meta-analyses are labor-intensive and prone to human error and bias[8]. AI can significantly enhance efficiency by automating time-consuming tasks such as data extraction, synthesis, and statistical analysis, thereby reducing the workload on researchers and accelerating the meta-analytical process.

Rayyan, an AI tool for screening systematic reviews, is frequently used in meta-analytical studies[15]. Robot Reviewer, a machine-learning tool, has been used to assess the risk of bias in clinical studies[16]. The reliability of Robot Reviewers was similar to that of human reviewers and, in some cases, better. ChatGPT has been reported as a powerful tool for intermediate researchers conducting epidemiological studies. However, applying more advanced statistical methods has limitations that require further consideration[17]. A major concern with AI-generated responses is the so-called black box. The black box indicates a system whose internal workings were not transparent. However, the same transparency argument may apply equally to human-generated analysis[18]. Therefore, pinpointing which technical modules of large language models require improvement to enhance the accuracy and reliability of pooled analyses across multiple studies remains challenging. It has yet to be determined whether large language models can effectively perform more complex statistical analyses, such as regression and matched analysis. Enhancing ChatGPT's statistical coding, data curation, and processing modules would likely refine these capabilities. However, AI-generated responses must still be validated and verified by human expertise. Since AI models rely on high-quality curated datasets, the outcome of one analysis may be biased by the results of prior studies. We propose improving data quality and developing robust training datasets to enhance the reliability of AI-driven analyses. Strengths and Limitations

A major strength of this study was its novelty. To the best of our knowledge, this study is the first to comparatively analyze AI-generated meta-analyses and traditional meta-analyses in the field of cardiology. Additionally, the study compared various effect sizes across diverse outcome measures, providing a thorough assessment of the reliability of the synthesis of the research results.

However, our study had several limitations that must be acknowledged. First, the analysis was confined to the field of cardiology, and the applicability of AI-generated meta-analyses to other medical disciplines remains to be explored. To counteract this and improve generalizability, we include multiple effect measures across a variety of randomly selected journals. Second, although the ChatGPT is a powerful language model, it has inherent limitations in handling complex statistical tasks. The ChatGPT is not designed to independently perform statistical analyses for meta-analyses or other intricate statistical computations. Moreover, it cannot directly access, manipulate, or analyze datasets, nor can it perform statistical computations such as calculating effect sizes or assessing heterogeneity. Third, the inclusion of only five studies at random may introduce potential bias. Finally, ChatGPT lacks the ability to independently validate results, handle missing data, check assumptions, and modify models based on intermediate results. These tasks require specialized statistical software and expert knowledge.

Our study serves as a pilot study and forms the basis for future research. Further exploration of the capabilities of ChatGPT in data synthesis is warranted, based on our results.

CONCLUSION

This study demonstrated the promising potential of ChatGPT in conducting meta-analyses. The overall concordance between the AI-generated and human-conducted analyses suggests that AI can be a valuable tool in this field. However, slight differences in CIs and *P* values persist, possibly due to different statistical models, or algorithm limitations. We believe that, at present, large language models such as ChatGPT cannot replace the structured and detailed statistical analysis required for rigorous research. Further research and development are essential for integrating AI into

mainstream medical research and practice.

FOOTNOTES

Author contributions: Goyal A designed research, performed research, analyzed data, and wrote the paper; Tariq MD performed research and analyzed data; Ahsan A wrote the paper; Khan MH wrote the paper; Zaheer A wrote the paper; Jain H wrote the paper; Maheshwari S supervised research, validated findings, and wrote the paper; Brateanu A supervised research, validated findings, conceptualized the study, and wrote the paper. Goyal A and Brateanu A are co-corresponding authors, as the former is expected to change their email and workplace in the near future. Since both authors contributed equally to the conceptualization and have a strong understanding of the topic, assigning two corresponding authors ensures smooth communication between journal readers and the authors in the future.

Conflict-of-interest statement: The authors have no conflicts of interest statement to declare.

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SYSTEMATIC REVIEWS

Navigating gastrointestinal challenges in genetic myopathies: Diagnostic insights and future directions

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Abstract

BACKGROUND

Gastrointestinal (GI) manifestations are prevalent in genetic myopathies, posing significant diagnostic and management challenges.

AIM

To synthesize evidence on the diagnostic approaches, management strategies, patient perspectives, and future research directions regarding GI symptoms in genetic myopathies.

METHODS

A systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. We searched PubMed, Scopus, EMBASE, and Web of Science from inception to December 2024. Eligible studies reported GI manifestations in genetic myopathies, including clinical evaluations,

imaging, physiological tests, histopathology, and genetic analyses. Inclusion criteria encompassed original research studies, review articles, case reports, and clinical guidelines published in peer-reviewed journals. Exclusion criteria included conference abstracts without full-text availability and non-peer-reviewed sources. Two independent reviewers screened studies and extracted data. They assessed methodological quality using the Newcastle-Ottawa Scale for observational studies, A MeaSurement Tool to Assess Systematic Reviews for systematic reviews, and the Joanna Briggs Institute checklist for case reports. A systematic narrative synthesis was employed to summarize the findings.

RESULTS

A total of 234 studies met the inclusion criteria. GI manifestations varied widely, with dysphagia, gastroesophageal reflux, abdominal pain, constipation, diarrhea, and fecal incontinence being the most frequently reported symptoms. The included studies highlighted a multidisciplinary diagnostic approach incorporating clinical assessment, imaging, physiological testing, histopathology, and genetic testing. Management strategies ranged from dietary interventions and rehabilitative therapies to pharmacological treatments and surgical procedures. Patient perspectives underscored the significant impact of GI symptoms on quality of life, social interactions, and emotional well-being. The main limitations of the included studies were high heterogeneity in study design, small sample sizes, and the potential risk of bias due to limited methodological rigor in some reports.

CONCLUSION

This review underscores the complexity of GI manifestations in genetic myopathies and the need for a comprehensive, multidisciplinary management approach. Future research should focus on elucidating molecular mechanisms, identifying biomarkers, and developing targeted therapies to improve patient outcomes. The findings have implications for both clinical practice and public health, emphasizing the necessity of early diagnosis and personalized management strategies.

Key Words: Genetic myopathies; Gastrointestinal manifestations; Diagnostic approaches; Multidisciplinary management; Patient perspectives; Future directions; Quality of life

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Core Tip: Gastrointestinal (GI) manifestations in genetic myopathies are frequently overlooked yet significantly impact patient outcomes. This systematic review highlights the prevalence, diagnostic challenges, and management strategies for GI dysfunction in conditions like Duchenne muscular dystrophy, Becker muscular dystrophy, and mitochondrial myopathies. The study underscores the role of imaging, motility testing, and genetic evaluation in guiding care. Additionally, it explores the influence of genetic and environmental modifiers on symptom variability. A multidisciplinary approach integrating gastroenterology, neurology, and nutrition is essential for improving quality of life. Future research should focus on targeted therapies and molecular mechanisms to optimize patient management.

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INTRODUCTION

Genetic myopathies are a group of inherited muscle disorders caused by genetic defects in the contractile fibers of the muscle, their membrane, or supporting proteins, leading to structural and functional abnormalities. These conditions vary widely in severity and presentation but typically involve progressive muscle weakness, atrophy, and impaired motor function[1]. The etiology of genetic myopathies depends on the specific condition but generally involves mutations in genes encoding structural proteins, enzymes involved in energy production, or proteins responsible for muscle regulation. These mutations disrupt normal muscle function, leading to the characteristic symptoms of the disorder[2]. Genetic myopathies are classified into muscular dystrophies, congenital myopathies, metabolic myopathies, myotonic disorders, and mitochondrial myopathies[3]. Although individually rare, collectively, these disorders impose a significant burden on affected individuals and their families[4]. The prevalence of genetic myopathies varies, with estimates ranging between 1:5000 and 1:50000, depending on the specific disorder and population[5].

Muscle weakness is the hallmark of genetic myopathies and can significantly impair daily activities such as walking, climbing stairs, and lifting objects. It may be generalized or localized, affecting specific muscle groups[6]. Prolonged muscle tightness and contractures can restrict joint mobility and flexibility, leading to skeletal deformities[7]. In severe cases, respiratory muscle weakness can result in breathing difficulties and life-threatening complications[8]. The impact

of genetic myopathies extends beyond skeletal muscle involvement, affecting multiple organ systems. As smooth muscle shares some structural similarities with skeletal muscle, genetic myopathies can also affect the gastrointestinal (GI) tract, leading to symptoms such as dysphagia, gastroesophageal reflux disease (GERD), constipation, and intestinal pseudo-obstruction[9]. GI manifestations in genetic myopathies are often underrecognized but significantly impact patients' quality of life, nutrition, and overall health[10].

Myopathies effects often extend beyond skeletal muscles to affect other organs or tissues as well. As smooth muscles share skeletal muscles with some common structural features, myopathies can impact the GI tract, leading to symptoms such as dysphagia, reflux, and constipation[11]. In some cases, individuals with myopathies may experience swallowing difficulties due to weakened or impaired muscles in the esophagus, leading to dysphagia[12]. Additionally, muscle weakness can affect the coordination of the digestive system, potentially causing issues such as GERD or constipation[13]. These GI symptoms can significantly impact the quality of life for individuals with myopathies, requiring mana-gement and support from healthcare professionals[14].

This review aims to explore the GI manifestations observed in genetic myopathies systematically. By elucidating the connection between inherited muscle disorders and GI symptoms such as dysphagia, GERD, constipation, diarrhea, and intestinal pseudo-obstruction, this review underscores the importance of recognizing and addressing these complications in clinical practice. Additionally, it highlights the necessity of a multidisciplinary approach involving specialists from neurology, gastroenterology, and nutrition to provide comprehensive care for affected individuals, thereby improving their overall well-being.

MATERIALS AND METHODS

This systematic review follows a comprehensive, multidisciplinary approach to investigating GI manifestations in genetic myopathies. The study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring methodological rigor and transparency.

A systematic literature search was performed using four electronic databases: (1) PubMed; (2) Scopus; (3) EMBASE; and (4) Web of Science. The search strategy combined Medical Subject Headings terms and free-text keywords related to genetic myopathies and GI manifestations. Boolean operators (AND, OR, NOT) were applied to refine the search. The following are examples of search terms used: ("Genetic myopathies" OR "muscular dystrophy" OR "mitochondrial myopathies" OR "congenital myopathies" OR "metabolic myopathies" OR "limb-girdle muscular dystrophy" OR "Duchenne muscular dystrophy" OR "Becker muscular dystrophy") AND ("Gastrointestinal manifestations" OR "dysphagia" OR "gastroparesis" OR "intestinal pseudo-obstruction" OR "malabsorption" OR "constipation" OR "gastroesophageal reflux disease" OR "abdominal pain" OR "bowel dysfunction"). The search was limited to studies published in peer-reviewed journals. The study design was not restricted, allowing the inclusion of primary research studies, review articles, case reports, and clinical guidelines.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) Focused on GI manifestations in genetic myopathies; (2) Provided original research findings, review articles, case reports, or clinical guidelines; (3) Published in peer-reviewed journals or reputable scientific sources; and (4) Available in full-text and written in English.

Studies were excluded if they met the following criteria: (1) Irrelevant to genetic myopathies or GI manifestations; (2) Duplicate publications from the same dataset without additional findings; (3) Conference abstracts without full-text availability; and (4) Non-peer-reviewed sources, including preprints, editorials, and letters.

Study selection

Screening and selection were performed in two phases: (1) Title and abstract screening: Two independent reviewers (Reviewer 1 and Reviewer 2) screened all retrieved articles based on the eligibility criteria; and (2) Full-text review: Articles that met the initial screening criteria were retrieved and reviewed in full text by the same two reviewers.

Discrepancies in study selection were resolved through discussion or, if necessary, consultation with a third reviewer. A PRISMA flow diagram (Figure 1) illustrates the study selection process.

Statistical analysis

Two independent reviewers performed data extraction using a standardized form. Extracted data included study characteristics (design, sample size, country of origin), patient demographics (age, sex, genetic diagnosis), GI symptoms and complications, diagnostic approaches and imaging modalities used, management strategies and interventions, and patient perspectives and quality-of-life impact.

To assess the methodological quality and risk of bias, we applied validated tools based on study design. Newcastle-Ottawa Scale was used for observational studies. A MeaSurement Tool to Assess Systematic Reviews was used for systematic reviews, while Joanna Briggs Institute's checklist was used for case reports. Studies were graded for quality, and those with a high risk of bias were excluded from the final analysis. Discrepancies in study selection, data extraction, and quality assessment were resolved by consensus or consultation with a third reviewer.

A systematic narrative synthesis was used to analyze findings, identifying common themes, trends, and gaps in the literature. Results were categorized based on GI symptoms, disease subtypes, and diagnostic and management strategies. Areas of consensus and controversies were discussed, and future research priorities were highlighted. Limitations of the included studies, such as risk of bias, small sample sizes, and variability in study design, were also considered in the

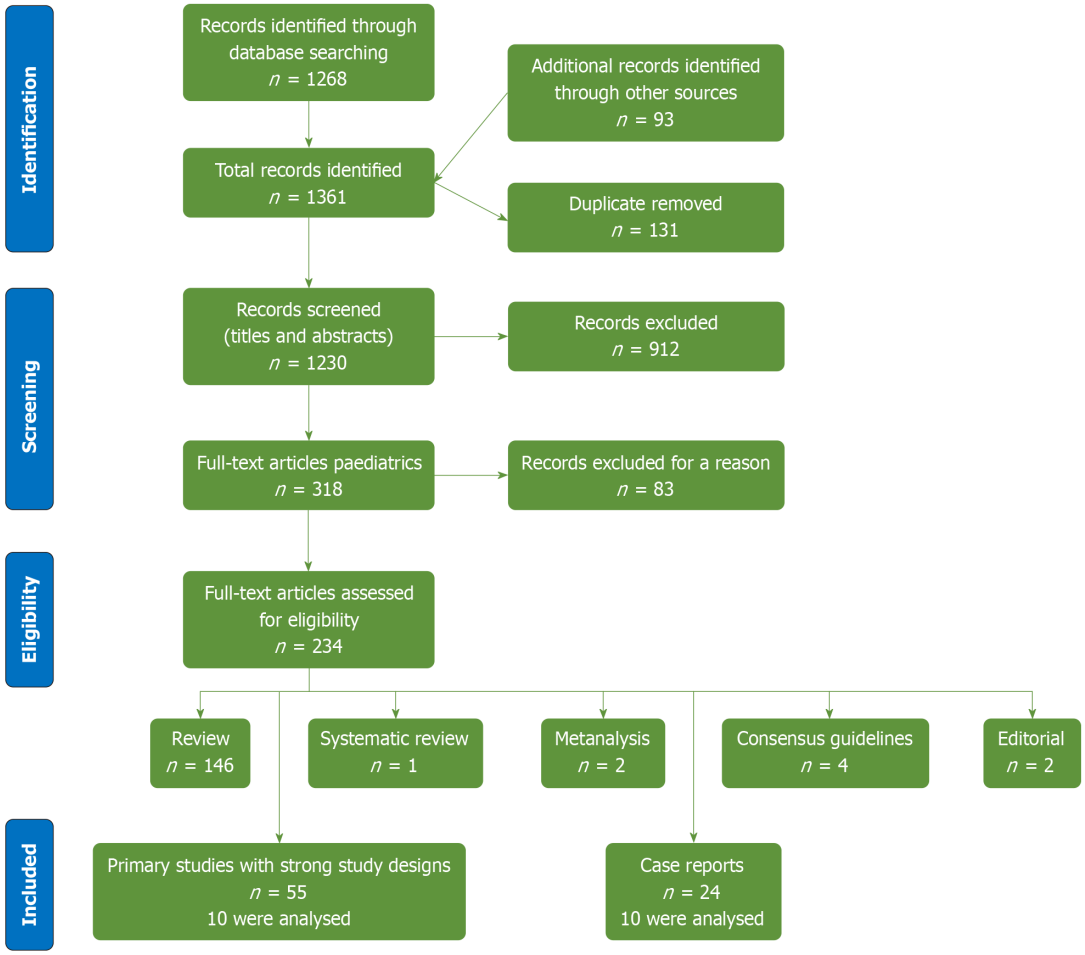


Figure 1 The flow chart of the included studies.

analysis. Since this study is based on previously published literature, ethical approval and patient consent were not required. However, ethical considerations included ensuring accuracy, transparency, and appropriate attribution of sources in reporting findings.

RESULTS

Figure 1 shows the study's flow chart. A total of 10 studies and 10 case reports met the inclusion criteria, describing GI manifestations in children with various types of genetic myopathies, including Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), limb-girdle muscular dystrophy (LGMD), myotonic dystrophy (DM) [type 1 (DM1) and DM type 2 (DM2)], nemaline myopathy, and mitochondrial disorders such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome and Kearns-Sayre syndrome. The included studies highlighted a multimodal diagnostic strategy for assessing GI dysfunction in genetic myopathies, incorporating clinical evaluation, imaging studies, physiological tests, histopathology, and genetic testing. Symptoms such as dysphagia, reflux, constipation, and pseudo-obstruction were commonly assessed *via* patient-reported outcomes and physical examination findings. Table 1 summarizes studies on GI manifestations in genetic myopathies[15-24]. The included studies primarily focused on DMD and other neuromuscular disorders, with a particular emphasis on dysphagia, motility disorders, and metabolic complications. Jaffe *et al*[15] demonstrated that DMD patients had higher rates of dysphagia, choking, and heartburn compared to controls, emphasizing the impact of oropharyngeal muscle weakness. Hilbert *et al*[16] found that 55% of DM1 patients had swallowing difficulties, while 53% of DM2 patients reported severe constipation. In addition, Tieleman *et al*[17] reported significant dysphagia, abdominal pain, and constipation in DM2 patients, suggesting GI involvement similar to DM1.

Other studies show significant GI dysmotility and constipation in patients with genetic myopathies. Lo Cascio *et al*[18] used objective motility tests to show delayed gastric emptying, prolonged oro-cecal transit, and slow colonic transit times in DMD patients, independent of symptom perception. In addition, Kraus *et al*[19] found that 46.7% of DMD patients had functional constipation, yet many remained undiagnosed and undertreated. Furthermore, Nart *et al*[20] described life-threatening colonic pseudo-obstruction and sigmoid volvulus in older DMD patients, highlighting the risks of advanced GI dysmotility. Metabolic and liver dysfunction are also common in genetic myopathies[20]. Kansu *et al*[21] showed that 47% of children with isolated hyper-transaminasemia had underlying DMD/BMD, reinforcing liver enzyme abnor-

Table 1 Summary of studies on gastrointestinal disorders in genetic myopathies

Ref.	Study title	Population	GI manifestations	Methods	Key findings
Jaffe *et al* [15], 1990	Symptoms of upper gastrointestinal dysfunction in Duchenne muscular dystrophy: Case-control study	55 DMD patients, 55 controls	Dysphagia, choking, heartburn, vomiting	Case-control study, questionnaire-based assessment	DMD patients had significantly more GI symptoms than controls, especially oropharyngeal dysfunction
Lo Cascio *et al*[18], 2016	Gastrointestinal Dysfunction in Patients with Duchenne Muscular Dystrophy	33 DMD patients (12-41 years)	Constipation, delayed gastric emptying, prolonged oro-cecal transit time	Questionnaires, gastric emptying time, colonic transit studies	DMD patients had prolonged gastric emptying and colonic transit times, indicating severe GI dysmotility
Lee *et al* [23], 2020	Relationship between Eating and Digestive Symptoms and Respiratory Function in Advanced Duchenne Muscular Dystrophy Patients	180 advanced DMD patients	Constipation, swallowing difficulty, aspiration	Questionnaires, respiratory function tests	GI symptoms correlated with respiratory function, not age, indicating progressive neuromuscular decline
Borrelli *et al*[24], 2005	Evolution of gastric electrical features and gastric emptying in children with Duchenne and Becker muscular dystrophy	20 children with DMD/BMD	Delayed gastric emptying, dysrhythmias	Electrogastrography, ultrasonography	DMD patients showed worsening gastric motility over time, BMD patients had milder symptoms
Kansu *et al* [21], 2023	The frequency of Duchenne muscular dystrophy/Becker muscular dystrophy and Pompe disease in children with isolated transaminase elevation: results from the observational VICTORIA study	589 children with elevated transaminases	Liver dysfunction, metabolic abnormalities	CPK testing, genetic analysis	DMD/BMD diagnosed in 47% of male patients with isolated hypertransaminasemia
Tang *et al* [22], 2022	Hepatic Steatosis Assessment as a New Strategy for the Metabolic and Nutritional Management of Duchenne Muscular Dystrophy	48 DMD patients	Metabolic syndrome, hepatic steatosis	Liver ultrasound, metabolic assessment	Total 40% of DMD patients had significant hepatic steatosis, increasing with disease progression
Kraus *et al* [19], 2016	Constipation in Duchenne Muscular Dystrophy: Prevalence, Diagnosis, and Treatment	120 DMD patients (5-30 years)	Functional constipation	Questionnaire, Bristol stool form scale, abdominal radiographs	Total 46.7% had functional constipation, often underdiagnosed and undertreated
Nart *et al* [20], 2023	Life-threatening bowel complications in adults with Duchenne muscular dystrophy: a case series	Adults with DMD	Colonic pseudo-obstruction, sigmoid volvulus	Case series, clinical review	Emphasized surgical risks and role of home parenteral nutrition
Hilbert *et al*[16], 2017	High frequency of gastrointestinal manifestations in myotonic dystrophy type 1 and type 2	913 DM1 and 180 DM2 patients	Dysphagia, constipation, cholecystectomy	Patient-reported surveys, medical records	DM1 had higher rates of swallowing issues, while DM2 had more constipation
Tieleman *et al*[17], 2008	Gastrointestinal involvement is frequent in Myotonic Dystrophy type 2	29 DM2 patients, 29 DM1 patients, 87 controls	Dysphagia, abdominal pain, constipation	Questionnaires, colon transit study	GI dysfunction was as common in DM2 as in DM1, with slow colonic transit in 24%

BMD: Becker muscular dystrophy; DM: Myotonic dystrophy; DMD: Duchenne muscular dystrophy; GI: Gastrointestinal.

malities as a potential early marker of muscle disease. In addition, Tang *et al*[22] reported 40% of DMD patients had hepatic steatosis, which worsened with disease progression and steroid use. These findings underscore the underrecognized role of GI dysfunction in genetic myopathies, emphasizing the need for early screening, dietary interventions, and multidisciplinary care.

Table 2 shows different case reports highlighting severe GI complications[25-34]. The case reports illustrated severe and often life-threatening GI manifestations, reinforcing the importance of early detection and intervention in patients with genetic myopathies. Acute gastric dilation and gastroparesis were observed in some patients with genetic myopathies. Dhaliwal *et al*[25] described a DMD patient with a gigantic stomach due to severe gastroparesis, managed conservatively. Barohn *et al*[26] documented gastric hypomotility and smooth muscle degeneration in a DMD patient with fatal acute gastric dilation.

Walsh *et al*[27] and Yoo *et al*[28] described cases with severe dysphagia and aspiration risk. Walsh *et al*[27] identified progressive dysphagia for solids and liquids in LGMD2B, confirmed *via* videofluoroscopy and genetic testing. Meanwhile, Yoo *et al*[28] reported swallowing difficulties and aspiration risks in nemaline myopathy, demonstrating the potential for improvement with dysphagia rehabilitation. On the other hand, Glaser *et al*[29], Bayoumy *et al*[30], and Sartoretti *et al*[31] described patients with different types of genetic myopathies who developed intestinal pseudo-obstruction and surgical emergencies. Glaser *et al*[29] presented a case of chronic intestinal pseudo-obstruction in DM, requiring colectomy for symptom relief. Bayoumy *et al*[30] described a 32-year-old woman with MD1 who developed sigmoid volvulus, successfully treated with endoscopic decompression. Sartoretti *et al*[31] reported a case of intestinal non-rotation and acute pseudo-obstruction in DM, which was managed conservatively, avoiding unnecessary surgery. Mitochondrial disorders and GI dysfunction were also observed in some patients with genetic myopathies. Dindyal *et al* [32] described MELAS syndrome presenting as toxic megacolon, necessitating emergency colectomy. Shaker *et al*[33] used

Table 2 Summary of case reports on gastrointestinal disorders in genetic myopathies

Ref.	Title of case report	Condition	Gastrointestinal manifestations	Management	Outcome
Dhaliwal *et al*[23], 2019	Gigantic Stomach: A Rare Manifestation of Duchenne Muscular Dystrophy	DMD	Severe gastric dilation, gastroparesis	Conservative management	Resolved without surgery
Barohn *et al* [24], 1988	Gastric Hypomotility in Duchenne's Muscular Dystrophy	DMD	Acute gastric dilation, intestinal pseudo-obstruction	Autopsy study, gastric emptying tests	Found smooth muscle degeneration
Xie *et al*[34], 2020	Transaminitis in a Three-year-old Boy with Duchenne Muscular Dystrophy	DMD	Elevated liver enzymes, metabolic dysfunction	Enzyme tests, genetic sequencing	Diagnosed early, no liver damage found
Walsh *et al* [25], 2011	Progressive dysphagia in limb-girdle muscular dystrophy type 2B	Limb-girdle muscular dystrophy 2B	Progressive dysphagia for solids and liquids	Videofluoroscopy, genetic analysis	Confirmed Dysferlin mutations as the cause
Yoo *et al*[26], 2022	Clinical Course of Dysphagia in Patients with Nemaline Myopathy	Nemaline myopathy	Swallowing difficulties, aspiration risk	Tube feeding, dysphagia therapy	Improved swallowing over time
Glaser *et al* [27], 2015	Myotonic dystrophy as a cause of colonic pseudoobstruction: not just another constipated child	Myotonic dystrophy	Chronic intestinal pseudo-obstruction	Colectomy	Successful surgical outcome
Bayoumy *et al*[28], 2022	Sigmoid Volvulus in Myotonic Dystrophy Type I (Steinert Disease)	DM1 (Steinert disease)	Sigmoid volvulus	Endoscopic decompression	Resolved with conservative management
Dindyal *et al* [30], 2014	MELAS syndrome presenting as an acute surgical abdomen	MELAS syndrome	Toxic megacolon	Total colectomy	Diagnosis confirmed postoperatively
Sartoretti *et al*[29], 1996	Intestinal non-rotation and pseudoobstruction in myotonic dystrophy: case report and review of the literature	DM	Acute abdomen, ileus, aspiration pneumonia	Conservative therapy	Avoided surgery, symptoms controlled
Shaker *et al* [31], 1992	Manometric characteristics of cervical dysphagia in a patient with the Kearns-Sayre syndrome	Kearns-Sayre syndrome	Dysphagia, upper esophageal sphincter dysfunction	Manometry	Confirmed pharyngeal and esophageal dysmotility

DM: Myotonic dystrophy; DMD: Duchenne muscular dystrophy; MELAS: Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

manometric studies to confirm pharyngeal and esophageal dysmotility in a patient with Kearns-Sayre syndrome. These case reports highlight the unpredictable and often severe nature of GI complications in myopathies, reinforcing the need for close monitoring, early intervention, and tailored management strategies.

Previous studies and case reports suggest that GI symptoms may precede neuromuscular diagnoses, particularly in disorders affecting smooth muscle function. Dysphagia and motility disorders are prevalent across all genetic myopathies, with a high burden in DMD, DM (DM1 and DM2), and nemaline myopathy. Constipation and severe dysmotility syndromes are common but often underdiagnosed and undertreated. Metabolic and hepatic complications are increasingly recognized in muscular dystrophies, requiring further research into their pathophysiology. Severe GI complications, such as acute gastric dilation, pseudo-obstruction, and volvulus, can be life-threatening and necessitate prompt intervention. The diagnostic evaluation involved clinical assessment, imaging studies [X-rays, ultrasound, computed tomography (CT)/magnetic resonance imaging (MRI)], physiological tests (manometry, pH monitoring, gastric emptying studies, anorectal manometry), histological analysis (endoscopic biopsy, muscle biopsy), and genetic testing [next-generation sequencing (NGS) panels].

Managing GI manifestations in genetic myopathies requires an individualized, multidisciplinary approach. Nutritional interventions such as tube feeding and dietary modifications were commonly recommended for dysphagia and malnutrition. Swallowing therapy and speech-language interventions improved feeding ability in patients with oropharyngeal dysphagia. Pharmacological treatments, including prokinetic agents, laxatives, and proton pump inhibitors (PPIs), were widely used to address delayed gastric emptying, constipation, and reflux, respectively. Severe cases required gastrostomy tube placement, colectomy, or endoscopic decompression for pseudo-obstruction and volvulus.

GI symptoms significantly affect quality of life, social interactions, and emotional well-being. Dysphagia and motility disorders contributed to nutritional deficiencies, requiring enteral feeding in advanced cases. Chronic constipation and pseudo-obstruction led to recurrent hospitalizations, reducing independence in daily activities. Many patients reported anxiety, embarrassment, and social withdrawal due to incontinence or feeding difficulties.

The findings highlight several critical gaps in understanding and managing GI dysfunction in genetic myopathies. Further research is needed to elucidate the role of smooth muscle dysfunction, autonomic nervous system involvement, and neuromuscular signaling in GI dysmotility. Identifying molecular or imaging biomarkers could improve early detection and monitoring. Investigating gene therapy, neuromodulation techniques, and pharmacological innovations may lead to better treatment outcomes. Establishing evidence-based recommendations for GI assessment and management protocols across different myopathy subtypes is necessary.

This review underscores the diverse and often severe nature of GI dysfunction in genetic myopathies, emphasizing the need for early screening, standardized diagnostic protocols, and a multidisciplinary management approach. Future research should focus on elucidating molecular mechanisms, identifying biomarkers, and developing targeted therapies to enhance patient outcomes and quality of life.

DISCUSSION

Types of genetic myopathies

Many types of genetic myopathies may involve the GI tract. Table 3 summarizes the main features of these myopathies. Muscular dystrophies involve various types of muscular dystrophies, such as DMD, BMD, and LGMD, which may exhibit GI manifestations[35]. DMD is the most common form of childhood muscular dystrophy, affecting approximately 1 in 3500 to 1 in 9300 male live births globally. This translates to a prevalence of 1-9 cases per 100000 individuals. DMD is an X-linked recessive genetic disorder caused by mutations in the dystrophin gene located on the X chromosome[36]. The dystrophin gene is one of the largest in the human genome, making it susceptible to various mutations. Deletions and duplications within the gene are the most common mutations, accounting for around 70%-80% of DMD cases. Point mutations (changes in single nucleotides) occur in 20%-30% of cases[37]. While most cases are due to inherited mutations, around 33% of DMD diagnoses arise from new mutations (not inherited from parents) occurring in the sperm or egg cell. Germline mosaicism (where only some of the egg or sperm cells have the mutation) can also contribute to DMD, even if parents do not have the condition[38].

BMD is a milder allelic form of DMD. It is less common than DMD, with a worldwide prevalence estimated at around 1-6 cases per 100000 individuals. This translates to 0.1-1.8 cases per 10000 male births. BMD shares the same genetic basis as DMD, with mutations occurring in the same dystrophin gene on the X chromosome. However, the type and severity of the mutations in the dystrophin gene differ between the two conditions[39]. In BMD, mutations are typically in-frame deletions, duplications, or small insertions. These mutations partially preserve the gene's reading frame, allowing some functional dystrophin protein to be produced. In contrast, DMD often results from out-of-frame mutations (deletions or duplications that disrupt the reading frame) or large deletions, leading to little or no functional dystrophin production [40]. BMD usually manifests later than DMD, typically in adolescence or early adulthood, compared to early childhood in DMD. BMD progresses slower and generally presents with milder symptoms compared to DMD. Individuals with BMD may experience progressive muscle weakness, fatigue, and difficulty with mobility, but the course and severity can vary considerably[41]. While muscle weakness can eventually impact different bodily functions, the life expectancy for individuals with BMD is generally longer compared to those with DMD. Similar to DMD, around 30% of BMD cases occur due to new mutations in the sperm or egg cell, and germline mosaicism can also contribute to the condition[42].

LGMD is a heterogeneous group of genetic muscle disorders characterized by progressive weakness primarily affecting the shoulder and pelvic girdle muscles. Determining the prevalence of LGMD is challenging due to its diverse forms and overlap with other muscle disorders. Estimates suggest a range of 1 in 14500 to 1 in 123000 individuals globally [43]. LGMD exhibits a complex genetic landscape, with multiple genes involved and different inheritance patterns. Broadly, LGMDs are categorized into two main types based on inheritance: (1) Autosomal dominant (LGMD1); and (2) Autosomal recessive (LGMD2)[44]. LGMD1 forms are less common, accounting for around 5%-10% of LGMD cases, and are caused by mutations in a single gene. Only one copy of the mutated gene from either parent is sufficient to cause the condition[45]. LGMD2 forms are more frequent, making up around 90% of LGMD cases. They require inheritance of two copies of the mutated gene, one from each parent. Over 50 genetic loci have been identified as potential contributors to various LGMD subtypes[46]. Each subtype can have its own specific gene and mutation responsible for the disease. Some frequently involved genes include *Lamin A/C* (*LMNA*), *Calpain 3* (*CAPN3*), and *Dysferlin* (*DYSF*). CAPN3 is responsible for LGMD2A, the most common subtype. DYSF is associated with LGMD2B, another prevalent form, while LMNA is involved in LGMD1B, a dominant form[47]. The specific gene responsible for an individual's LGMD depends on the specific type and family history. New gene discoveries are ongoing, and further research is needed to fully understand the complete spectrum of genes and mutations contributing to LGMD[45].

Congenital myopathies are a diverse group of structural muscle disorders present at birth or infancy, with different types of varying presentations. Muscle fiber architectural abnormalities are the hallmark of congenital myopathies. According to predominant structural pathological muscle abnormalities, these myopathies are divided into five subgroups: (1) Core myopathies (the most common form of congenital myopathies); (2) Nemaline myopathies; (3) Centronuclear myopathies; (4) Congenital fiber type disproportion myopathy; and (5) Myosin storage myopathy[44]. Early symptoms can be subtle and overlap with other conditions[48]. They have a pooled prevalence of around 1.62 per 100000 individuals, with a higher prevalence in children (around 2.76 per 100000)[49]. Like other muscular dystrophies, their genetic basis is complex and heterogeneous, involving mutations in over 40 genes with various inheritance patterns. Broadly, the inheritance patterns can be categorized as autosomal dominant (20%), autosomal recessive (most common, around 60%-70% of cases), and X-linked (less frequent)[50]. These mutations disrupt proteins essential for muscle development and function, leading to various types of congenital myopathies with varying symptoms like weakness, stiffness, and respiratory problems. Common mutations observed in these types of myopathies include *alpha-actine* (*ACTA1*) gene mutations, which are responsible for the common type "nemaline myopathy "with characteristic muscle weakness and stiffness[51]. Another mutation is the *RYR1* gene mutation, which causes "central core myopathy", leading to muscle weakness and hypotonia. *Dynamin 2* (*DNM2*) gene mutations are associated with "centronuclear myopathy", characterized by muscle weakness, respiratory problems, and intellectual disability. While genetic testing can help identify the specific type and inheritance pattern, in many cases, new gene discoveries continue to be made. Not all cases

Table 3 Overview of each type of genetic myopathy, including prevalence rates, age, sex, genetic bases, key clinical features, diagnostic approaches, and management strategies

Type of myopathy	Prevalence	Age of onset	Sex	Most affected races	Genetic basis	Key clinical features	Diagnostic approaches	Management strategies
DMD	1 in 3500 to 1 in 9300 male births globally	Early childhood	Males	All races, more common in certain populations such as Caucasian and African American	X-linked recessive genetic disorder caused by mutations in the dystrophin gene located on the X chromosome. Mutations include deletions, duplications, and point mutations	Muscle weakness, delayed motor milestones, dysphagia, GERD, delayed gastric emptying, constipation, pseudo-obstruction	Magnetic resonance imaging for smooth muscle atrophy, gastric emptying scintigraphy, genetic testing for dystrophin mutations	Swallowing therapy, proton pump inhibitors, dietary modifications, fundoplication for severe GERD
Becker muscular dystrophy	1–6 per 100000 individuals	Adolescence or early adulthood	Males	All races, more common in certain populations such as Caucasian and African American	Milder allelic form of DMD, also caused by mutations in the dystrophin gene, typically in-frame deletions, duplications, or small insertions, allowing some functional dystrophin protein to be produced	Similar to DMD but milder and later onset; dysphagia, GERD, delayed gastric emptying, fatty liver disease	Upper GI series, abdominal ultrasound for hepatomegaly, genetic testing	Nutritional support, laxatives for constipation, hepatoprotective agents
LGMD	1 in 14500–123000 globally	Varies (typically adolescence or adulthood)	Both sexes	All races	A heterogeneous group of disorders categorized into autosomal dominant (LGMD1) and autosomal recessive (LGMD2) forms involving mutations in various genes such as *Lamin A/C*, *Calpain 3*, and *Dysferlin*. Over 50 genetic loci were identified as potential contributors	Weakness in shoulder and pelvic girdle muscles, dysphagia, constipation, elevated liver enzymes	Esophageal manometry, liver ultrasound	Dietary fiber, biofeedback therapy for bowel dysfunction
Congenital myopathies	1.62 per 100000 globally (higher in children)	Present at birth or infancy	Both sexes have a higher prevalence in children	All races	A diverse group of disorders present at birth or infancy, caused by mutations in over 40 genes with various inheritance patterns, including *ACTA1*, *RYR1*, and *Dynamin 2*	Muscle hypotonia, delayed motor milestones, feeding difficulties, dysphagia, GERD, constipation, recurrent respiratory infections	Muscle biopsy, barium swallow, upper GI endoscopy	Feeding therapy, nutritional support, reflux management, respiratory care
Metabolic myopathies	1 in 5000 to 1 in 50000 individuals	Varies (childhood or adulthood)	Both sexes	All races	Caused by gene mutations affecting carbohydrate or fat metabolism within muscle cells, leading to disorders such as McArdle disease (*PYGM* gene) and Tarui disease (*PFKM* gene)	Exercise intolerance, muscle cramps, recurrent abdominal pain, nausea, diarrhea, fatty liver, hypoglycemia, hepatomegaly	Genetic panels, metabolic tests (*e.g.*, carnitine palmitoyltransferase or very long-chain acyl-CoA dehydrogenase), gastric motility studies	Dietary adjustments, enzyme replacement (*e.g.*, pancreatic enzymes), glucose infusions for hypoglycemia
Mitochondrial myopathies	1 in 5000 to 1 in 10000	Varies (childhood or adulthood)	Both sexes	All races	Result from mutations in genes involved in mitochondrial function and energy production, including MT-TL1 (mitochondrial encephalomyopathy,	Dysphagia, diarrhea, gastroparesis, pancreatitis, pseudo-obstruction, hepatopathy, malabsorption	Muscle biopsy, genetic testing for mitochondrial DNA mutations, gastric motility studies	Prokinetic agents, pancreatic enzyme replacement, nutritional supplementation

					lactic acidosis, and stroke-like episodes syndrome), MT-TK (myoclonic epilepsy with ragged red fibers syndrome), and sea urchin retroposon family 1 (Leigh syndrome). Inheritance can be autosomal recessive or matrilineal (mitochondrial DNA mutations)			
Myotonic disorders	1 in 8000 to 1 in 20000 globally	Typically adulthood	Both sexes	All races	This includes DM Type 1 (DM1) and Type 2 (DM2), caused by expanded CTG repeats in the *DMPK* gene and CCTG repeats in the *ZNFN213* gene, respectively. Autosomal dominant inheritance pattern	Dysphagia, GERD, constipation, paralytic ileus, diarrhea, megacolon, sigmoid volvulus, anal incontinence	Radiologic studies for motility, manometry, genetic testing for *DMPK* and *ZNFN213* genes	Swallowing therapy, dietary modifications, management of motility disorders, surgical interventions for volvulus or megacolon

DM: Myotonic dystrophy; DMD: Duchenne muscular dystrophy; *DMPK*: *Dystrophia myotonica protein kinase*; GERD: Gastroesophageal reflux disease; GI: Gastrointestinal; LGMD: Limb-girdle muscular dystrophy.

have a currently known genetic cause[52].

Metabolic myopathies are a diverse group of genetic muscle disorders characterized by abnormalities in the metabolism of carbohydrates or fats within muscle cells. These disorders can lead to muscle weakness, cramping, pain, and fatigue during exercise or even at rest[53]. The prevalence of metabolic myopathies varies depending on the specific type, but they are generally considered rare conditions. Estimates suggest a prevalence ranging from 1 in 5000 to 1 in 50000 individuals, with a higher likelihood of being diagnosed in adults than children[54]. The genetic basis of metabolic myopathies is also diverse, with mutations in multiple genes responsible for different metabolic myopathy types. These mutations typically affect enzymes crucial for metabolizing carbohydrates or fats for energy production or protein transporters, which are responsible for transporting essential molecules across the cell membrane[55]. The specific inheritance pattern can vary depending on the involved gene and can be autosomal recessive, autosomal dominant, or X-linked. Fatty acid oxidation disorders (FAOD) and glycogen storage diseases (GSDs) are common examples of metabolic myopathies[56]. GSDs are a group of disorders characterized by glycogen accumulation (a form of stored glucose) in muscle cells. Several subtypes of GSDs, including GSD type V (McArdle disease) and GSD type VII (Tarui disease), are caused by mutations in the *PYGM* and *PFKM* genes, respectively[57]. FAODs result from defects in the enzymes responsible for breaking down fatty acids for energy production. Deficiencies in enzymes such as carnitine palmitoyltransferase (CPT) or very long-chain acyl-CoA dehydrogenase (VLCAD) can lead to FAODs[58].

Mitochondrial myopathies are a group of genetic disorders that primarily affect mitochondria, which are the energy-producing structures within cells. These disorders result from mutations in genes involved in mitochondrial function and energy production[59]. Mitochondrial myopathies can affect various organs and tissues, but they primarily impact skeletal muscles, leading to muscle weakness, exercise intolerance, and other symptoms. Estimating the exact prevalence of mitochondrial myopathies is challenging due to the heterogeneity of the clinical presentations, the varying degrees of severity, and the difficult diagnosis due to symptoms overlapping with other disorders, leading to underdiagnosis. However, the prevalence of mitochondrial myopathies is expected to be around 1 in 5000 to 1 in 10000 individuals, making them relatively rare conditions[60]. However, the exact prevalence can vary depending on the specific subtype of mitochondrial myopathy and the population being studied. While the overall number might seem low, it's important to remember that mitochondrial disorders are among the most common genetic diseases[61]. Mitochondrial myopathies have a diverse genetic basis. They can be caused by mutations in genes located in either the nuclear DNA or the mitochondrial DNA (mtDNA). Nuclear DNA mutations are inherited in an autosomal recessive or autosomal dominant manner, while mtDNA mutations are typically inherited from the mother and follow a matrilineal pattern. The maternal inheritance has varying degrees of penetrance, expression of the disease, and clinical severity within families[62].

Several subtypes of mitochondrial myopathies are associated with specific gene mutations. Some of the commonly known forms include MELAS syndrome, myoclonic epilepsy with ragged red fibers (MERRF) syndrome, and Leigh syndrome. MELAS syndrome is often caused by a mutation in the *MT-TL1* gene, which produces a transfer RNA molecule involved in protein synthesis within mitochondria[60]. MERRF syndrome is typically caused by mutations in the *MT-TK* gene, leading to impaired mitochondrial protein synthesis[63]. Leigh syndrome can have multiple genetic causes, with mutations occurring in genes involved in mitochondrial energy production, such as the *sea urchin retroposon family 1*, *NADH dehydrogenase Fe-S protein 1*, and *adenosine triphosphate* (*ATP*) *6* genes[64]. In addition to these specific subtypes, there are many other less common forms of mitochondrial myopathies, each with its own genetic basis. Diagnosis of mitochondrial myopathies involves a combination of clinical evaluation, biochemical testing, muscle biopsies, and genetic testing. Genetic testing can help identify specific mutations and confirm the diagnosis[65].

Myotonic disorders (myotonic dystrophies) are a group of inherited neuromuscular diseases characterized by muscle stiffness, weakness, and wasting. Unlike most muscular dystrophies, which primarily cause muscle wasting and weakness, myotonic disorders often manifest with muscle stiffness and impaired relaxation after contraction (myotonia) [66]. Estimating the true prevalence of myotonic disorders is challenging due to the heterogeneity of presentations and severity and frequent mis/or underdiagnosis. However, estimates suggest a combined prevalence of 1 in 8000 to 1 in 20000 individuals globally, with specific types having variable frequencies[67]. DM1 is considered the most common form, with a prevalence of around 1 in 8000 individuals worldwide. It is caused by an expanded CTG repeat mutation in the *dystrophia myotonica protein kinase* (*DMPK*) gene on chromosome 19. This repeat expands in length across generations, leading to progressive worsening of symptoms. The number of CTG repeats is directly associated with the disorder's severity and age of onset[68]. DM2 is less common than DM1, with the exact prevalence unknown, and could be around 1 in 30000 to 1 in 100000 individuals, but potentially could be as frequent as DM1 in specific populations like Finland and Germany. It is caused by an expansion of CCTG repeats in the *ZNFN213* gene on chromosome 3. Similar to DM1, the number of CCTG repeats correlates with the severity and age of onset[69]. DM2 also follows an autosomal dominant inheritance pattern. This mutation also tends to expand with each generation. Both DM1 and DM2 follow an autosomal dominant inheritance pattern. This means that inheriting only one copy of the mutated gene from a parent is sufficient to cause the disorder[70]. However, the severity of symptoms can vary significantly due to factors like the length of the repeat expansion and other genetic modifiers. The complex interplay of repeat expansions, other genetic factors, and environmental triggers contribute to the diverse clinical presentations and disease progression[71]. Diagnosis of myotonic disorders involves a combination of clinical evaluation, family history assessment, electromyography to detect myotonia, and genetic testing to confirm the presence of the specific genetic mutation[72]. Management of myotonic disorders is primarily focused on symptom relief and optimizing quality of life. Treatment may involve physical therapy to manage muscle weakness and stiffness, medication to address symptoms such as myotonia and cardiac abnormalities, and regular monitoring of potential complications in organs such as the heart and respiratory system[73].

Molecular changes in genetic myopathies

DMD is primarily caused by mutations in the dystrophin gene, leading to the dystrophin protein's absence or dysfunction. However, the pathophysiology of DMD involves a complex interplay of molecular events beyond dystrophin deficiency. The absence or deficiency of the dystrophin protein, a critical component of the dystrophin-glycoprotein complex responsible for maintaining muscle membrane integrity, is the hallmark molecular abnormality in DMD[74]. Dystrophin deficiency compromises the stability of muscle fibers, making them susceptible to damage and degeneration. Transcriptomic studies have revealed widespread dysregulation of gene expression in DMD muscle tissue[75]. The upregulation of genes associated with inflammation, fibrosis, and muscle regeneration coexists with the downregulation of genes involved in muscle structure and function. This dysregulated gene expression contributes to the progressive loss of muscle mass and function in DMD[76]. Apart from dystrophin, DMD is associated with abnormal expression and localization of various proteins involved in muscle physiology. Disruptions in the expression and function of sarcolemmal proteins, cytoskeletal components, and signaling molecules contribute to muscle fiber fragility and impaired contractile function[77]. Dysregulation of signaling pathways plays a pivotal role in DMD pathogenesis. Aberrant activation of pathways such as nuclear factor-kappa B (NF-κB), transforming growth factor-beta (TGF-β), and Wnt/β-catenin signaling exacerbates DMD-associated inflammation, fibrosis, and degeneration. Conversely, impaired signaling cascades involved in muscle regeneration and repair further compromise muscle function[78]. Molecular changes in DMD have profound downstream effects on cellular processes such as inflammation, fibrosis, oxidative stress, and mitochondrial dysfunction. Chronic inflammation and fibrosis exacerbate muscle damage, while oxidative stress and mitochondrial dysfunction contribute to energy imbalance and impaired muscle function[79].

BMD is characterized by distinct molecular changes contributing to disease pathogenesis and progression. BMD arises from mutations in the dystrophin gene, producing truncated or partially functional dystrophin protein. Unlike DMD, where mutations lead to the absence of dystrophin, BMD mutations allow for some dystrophin production[77]. The severity of BMD is influenced by the extent of dystrophin deficiency and the specific mutation involved. Mutations in the dystrophin gene lead to aberrant expression and function of the dystrophin protein[80]. While dystrophin is produced in BMD, it is often reduced in quantity and compromised in function. This partial dystrophin expression contributes to muscle fiber instability and degeneration, albeit to a lesser extent than in DMD[41]. Transcriptomic analyses have revealed dysregulated gene expression patterns in BMD muscle tissue. The altered gene expression in muscle structure, metabolism, and signaling pathways contributes to disease pathogenesis. However, gene expression changes in BMD are typically less pronounced than those observed in DMD, reflecting the milder clinical phenotype[76]. Dysregulation of protein-protein interactions and signaling pathways is crucial in BMD pathogenesis. Abnormalities in the dystrophin-associated protein complex disrupt sarcolemmal integrity and intracellular signaling, contributing to muscle weakness and degeneration. Dysregulated signaling pathways such as NF-κB and TGF-β exacerbate inflammation, fibrosis, and muscle wasting in BMD[81]. Molecular changes in BMD have downstream effects on cellular processes such as inflammation, fibrosis, oxidative stress, and muscle regeneration. These processes contribute to disease progression, albeit at a slower rate compared to DMD. Additionally, compensatory mechanisms and enhanced muscle regeneration may partially mitigate the deleterious effects of molecular changes in BMD[82].

LGMD is a condition that causes disruptions in the normal functioning of muscle cells. These disruptions are usually caused by mutations in genes crucial for muscle structure, repair, and contraction[43]. These mutations can affect genes that encode important proteins like dystrophin, sarcoglycans, DYSF, calpain, or laminin, leading to compromised muscle fiber stability, impaired muscle membrane integrity, and abnormal calcium homeostasis[83]. LGMD2A is caused by mutations in the *CAPN3* gene, impacting a crucial protein in maintaining muscle structure. LGMD2B, on the other hand, is caused by mutations in the *DYSF* gene, which affects a protein involved in membrane repair and signaling pathways in

muscle cells[84]. Finally, LGMD1B results from mutations in *LMNA* genes, which affect muscle cell gene expression and function by affecting proteins essential for maintaining the nuclear envelope. These disruptions increase the likelihood of muscle damage, impaired muscle regeneration, and, ultimately, progressive muscle wasting and weakness[85]. Inflammatory processes and oxidative stress also contribute to developing LGMD, worsening muscle damage. The specific molecular mechanisms that cause the different subtypes of LGMD can vary, reflecting the diverse genetic causes and underlying pathways involved[86]. Understanding these molecular changes is crucial for developing targeted therapies and interventions to halt or slow the progression of LGMD.

Congenital myopathies arise from mutations affecting genes encoding proteins crucial for skeletal muscle structure, function, and regulation. Mutations in genes such as *ACTA1*, *RYR1*, MTM1, and *selenoprotein N* have been implicated in various forms of congenital myopathies, including nemaline myopathy, central core disease, myotubular myopathy, and congenital fiber-type disproportion[87]. Molecular studies have revealed diverse mechanisms contributing to muscle dysfunction, including disruption of sarcomere organization, impaired calcium handling, defective protein synthesis, and altered oxidative metabolism[88]. Dysregulation of signaling pathways involved in muscle development, such as the RhoA-ROCK pathway, has also been implicated in the pathogenesis of congenital myopathies[2]. Furthermore, advances in NGS technologies have facilitated the identification of novel disease-associated genes and variants, expanding our understanding of the genetic landscape of congenital myopathies[89].

Metabolic myopathies typically result from mutations affecting genes encoding enzymes critical for energy production, including those involved in glycolysis, glycogen metabolism, and fatty acid oxidation[86]. For example, enzyme deficiencies such as CPT and VLCAD lead to FAODs. In contrast, enzyme defects like glycogen phosphorylase or branching enzymes cause GSDs[90]. Molecular studies have uncovered various pathogenic mechanisms contributing to muscle dysfunction in metabolic myopathies, including impaired energy production, mitochondrial dysfunction, oxidative stress, and altered cellular signaling[91]. Disrupted metabolic pathways result in an inadequate supply of ATP, leading to muscle weakness, cramping, pain, and fatigue during exercise or even at rest. Additionally, aberrant lipid accumulation, mitochondrial abnormalities, and altered redox homeostasis contribute to muscle damage and inflammation[92].

Mitochondrial myopathies arise from mutations affecting genes encoding proteins involved in mitochondrial function, including those required for oxidative phosphorylation, mitochondrial protein synthesis, and mtDNA maintenance[61]. Molecular studies have revealed diverse mechanisms contributing to muscle dysfunction in mitochondrial myopathies, including impaired ATP production, mitochondrial respiratory chain dysfunction, oxidative stress, and mtDNA mutations[93]. These molecular changes lead to energy depletion, mitochondrial dysfunction, and cellular damage, particularly in tissues with high energy demands, such as skeletal muscle. Additionally, mitochondrial dysfunction triggers secondary processes such as inflammation, apoptosis, and oxidative damage, exacerbating muscle pathology[94].

Myotonic disorders, including DM1 and DM2, are caused by expanded repeat sequences in specific genes, leading to toxic RNA gain-of-function effects. In DM1, an expanded CTG repeat in the *DMPK* gene on chromosome 19 leads to the accumulation of mutant DMPK mRNA containing CUG repeats[95]. This expanded RNA forms toxic RNA foci, sequestering RNA-binding proteins such as muscleblind-like 1 and disrupting their normal cellular functions. The expanded CUG repeats are also processed into toxic microRNA-like molecules, further contributing to RNA toxicity[96]. In DM2, an expanded CCTG repeat in the *cellular nucleic acid protein* (*CNBP*) gene on chromosome 3 leads to the accumulation of mutant CNBP mRNA containing CCUG repeats. Like DM1, the expanded CCUG repeats form toxic RNA aggregates that sequester muscle blind-like proteins, impairing their splicing regulation functions[97]. Furthermore, dysregulation of alternative splicing and gene expression contributes to disease pathogenesis in myotonic disorders[98]. Molecular studies have also identified downstream cellular pathways affected by RNA toxicity, including dysregulation of ion channels, muscle development, and metabolism. Additionally, impaired insulin signaling and mitochondrial dysfunction have been implicated in the metabolic abnormalities observed in myotonic disorders[99].

Similarities and dissimilarities between skeletal and GI smooth muscles

The structure and bio-physiology of GI smooth muscles are finely tuned to orchestrate digestion, absorption, and waste elimination processes within the GI tract. These muscles are vital in maintaining GI function and overall digestive health [100]. Structurally, GI smooth muscles consist of spindle-shaped cells with a single nucleus, organized into two main layers: (1) The inner circular layer; and (2) The outer longitudinal layer. These layers work in tandem to facilitate peristalsis and other digestive processes. Additionally, specialized cells known as Interstitial Cells of Cajal serve as pacemakers, coordinating rhythmic contractions throughout the GI tract[101]. Various stimuli, including neural, hormonal, and mechanical signals, initiate smooth muscle contraction in the GI tract. Intracellular calcium concentration is crucial in triggering muscle contraction by activating the interaction between actin and myosin filaments[102]. The enteric nervous system, embedded within the GI tract wall, regulates smooth muscle activity, coordinating peristalsis, secretion, and blood flow. Neurotransmitters such as acetylcholine, serotonin, nitric oxide, and hormones like gastrin and motilin modulate smooth muscle contraction and relaxation, fine-tuning GI function[103]. Pacemaker activity generated by Cells of Cajal produces slow electrical waves propagating through GI smooth muscles, orchestrating rhythmic contractions. These slow waves are subject to modulation by neural and hormonal inputs, regulating the frequency and strength of contractions. GI smooth muscles demonstrate plasticity and adaptability, adjusting their contractile activity in response to changes in luminal contents and functional demands[104]. Functionally, GI smooth muscles perform crucial roles in digestion, absorption, and waste elimination. Peristalsis, coordinated contractions of smooth muscles, propels luminal contents forward through the digestive tract, facilitating digestion and absorption[105]. Alternating contractions and relaxations of smooth muscles facilitate the mixing of luminal contents with digestive enzymes, aiding in nutrient absorption. Additionally, smooth muscles regulate sphincter control, controlling the flow of luminal contents between different digestive compartments. Basal tone in GI smooth muscles helps maintain luminal patency and prevent reflux of

contents between digestive compartments[106].

Skeletal and GI smooth muscles share similarities and differences, as shown in Table 4. Both types of muscles are excitable tissues. They can respond to stimuli and generate electrical signals (action potentials) that trigger contraction. Both types of muscles contain actin and myosin filaments, the primary contractile proteins responsible for muscle contraction. Both have sarcoplasmic reticulum, a specialized network that stores calcium ions (Ca^{2+}), essential for initiating muscle contraction[107]. Both types of muscles contract through the sliding filament mechanism, where actin and myosin filaments slide past each other to generate force and produce muscle contraction. Skeletal and smooth muscles rely on calcium ions for muscle contraction. Increasing intracellular calcium concentration triggers muscle contraction by activating the interaction between actin and myosin filaments[108]. While the nervous system plays a significant role in regulating skeletal muscle contraction through motor neurons, GI smooth muscles also receive innervation from the autonomic nervous system, particularly the enteric nervous system, which modulates muscle activity and peristalsis[103]. Hormonal signals can influence both skeletal and GI smooth muscles. Hormones such as adrenaline and noradrenaline can affect the contractility of skeletal muscles, while GI hormones like gastrin and motilin regulate the activity of smooth muscles in the digestive tract[109].

On the other hand, there are many differences between the two types of muscles. For example, the skeletal muscles are under voluntary control and attached to bones, which can be consciously controlled to move. In contrast, GI smooth muscles are under involuntary control, and their contractions are not consciously regulated[110]. Meanwhile, skeletal muscles comprise multinucleated muscle fibers organized into distinct bundles, whereas GI smooth muscles consist of spindle-shaped cells with a single nucleus arranged in sheets or layers. Skeletal muscles typically contract rapidly and with greater force, enabling quick movements such as running or jumping[111]. GI smooth muscles contract more slowly, sustainably, and rhythmically, facilitating processes like peristalsis and mixing of digestive contents. Skeletal muscle relies primarily on anaerobic respiration for short bursts of activity, while smooth muscle primarily uses aerobic respiration for sustained contractions[105]. Skeletal muscle has limited regeneration abilities, while smooth muscle has a better capacity for self-repair. In addition, skeletal muscles exhibit varying degrees of fatigue during sustained activity due to the accumulation of metabolic by-products[112]. In contrast, GI smooth muscles are highly resistant to fatigue and can sustain prolonged contractions without significant energy depletion. Lastly, skeletal muscle contraction is primarily controlled by neural signals from the central nervous system, allowing for precise and coordinated movements[113]. GI smooth muscles can exhibit spontaneous contractions independent of neural input, driven by pacemaker cells and local neurotransmitters within the enteric nervous system[114].

General mechanisms of GI manifestations in genetic myopathies

The GI tract plays a crucial role in digestion, nutrient absorption, and waste elimination, which are regulated by neurogenic and myogenic factors. Proper gut motility, driven by coordinated contractions of smooth muscle cells lining the GI tract, is essential for the consumption and digestion of food, absorption of water and nutrients, and excretion of waste products[115]. Disruption of the autonomic or enteric nervous system, responsible for inducing smooth muscle contractions or dysfunction in the contractile network of smooth muscle cells, can significantly impact GI tract function. Consequences of such dysfunction include aspiration of food bolus into the lungs, retention of digesting material in the gut lumen, dehydration, fecal incontinence, and other complications[11]. Severe impairment disrupts daily activities and affects mental and emotional well-being. Maintaining the integrity of the neurogenic and myogenic regulatory systems governing GI tract motility is crucial for overall GI health and quality of life[116].

Genetic myopathies can present with various GI manifestations, impacting digestion, absorption, and waste elimination. The mechanisms underlying GI manifestations in genetic myopathies can be multifactorial and involve both structural and functional abnormalities of smooth muscles within the GI tract (Table 5). Smooth muscles play a crucial role in regulating the movement and function of the digestive system, including peristalsis, sphincter control, and mixing of food contents[83]. In genetic myopathies, mutations affecting the structure or function of smooth muscle cells can lead to abnormalities in GI motility and function. One key mechanism is the impairment of contractility in smooth muscle cells [117]. Genetic mutations may disrupt smooth muscles' normal contractile machinery, leading to muscle tone, coordination, and relaxation abnormalities. This can result in dysphagia (difficulty swallowing), GERD, gastroparesis, bloating, abdominal pain, constipation, diarrhea, and intestinal pseudo-obstruction, which are common GI manifestations observed in genetic myopathies[118]. Another mechanism is the involvement of skeletal muscle abnormalities in the muscles responsible for the voluntary control of the GI tract, such as the muscles of the pelvic floor and the external anal sphincter. Dysfunction in these muscles can lead to fecal incontinence and difficulty with bowel movements[119]. Impaired abdominal wall movement due to weak abdominal muscles can hinder the effectiveness of pushing stool during defecation. Weak muscles of mastication cause difficulty chewing and swallowing, leading to inadequate food intake and potential malnutrition[120].

Additionally, abnormalities in smooth muscle innervation and neuromuscular transmission can contribute to GI dysfunction in genetic myopathies. The enteric nervous system, which controls GI motility and secretion, may be affected by genetic mutations, leading to dysregulation of smooth muscle activity, and causing symptoms like diarrhea or constipation[121]. Furthermore, various neurotransmitters, hormones, and signaling pathways regulate smooth muscle cells in the GI tract. Disruption of these regulatory mechanisms due to genetic mutations can result in aberrant smooth muscle contraction and relaxation patterns, further contributing to GI symptoms[122]. Furthermore, certain genetic myopathies are associated with systemic manifestations, including metabolic abnormalities and endocrine dysfunction. These systemic abnormalities can indirectly impact the GI tract and contribute to GI symptoms[123]. For example, disturbances in energy metabolism or hormonal imbalances can affect gut motility and nutrient absorption[124]. Chronic GI problems in genetic myopathies can lead to malabsorption of essential nutrients due to impaired digestion and absorption. This can result in deficiencies of vitamins, minerals, and electrolytes, further impacting overall health and

Table 4 Skeletal *vs* gastrointestinal smooth muscle: Similarities and dissimilarities

Feature	Skeletal muscle	Gastrointestinal smooth muscle
Excitable tissue	Yes	Yes
Contractile proteins	Actin and myosin	Actin and myosin
Sarcoplasmic reticulum	Yes	Yes
Contraction mechanism	Sliding filament	Sliding filament
Calcium dependence	Yes	Yes
Control	Voluntary	Involuntary
Innervation	Motor neurons	Autonomic nervous system
Hormonal regulation	Yes	Yes
Attachment to bone	Yes	No
Fiber nuclei	Multinucleated	Uninucleated
Fiber arrangement	Bundles of striated (striped) fibers	Sheets or layers of non-striated fibers
Contraction speed	Fast and powerful	Slow and sustained
Contraction pattern	Brief bursts	Tonic (sustained)
Dominant respiration	Anaerobic	Aerobic
Regeneration	Limited	Better capacity
Fatigue resistance	Susceptible	Highly resistant
Main control system	Central nervous system	Enteric nervous system

Table 5 Mechanism of gastrointestinal manifestations in genetic myopathies

Mechanism	Description
Smooth muscle dysfunction	Genetic mutations affecting smooth muscle cells can lead to contraction, coordination, and relaxation abnormalities, resulting in dysphagia, gastroesophageal reflux disease, gastroparesis, bloating, abdominal pain, constipation, diarrhea, and intestinal pseudo-obstruction
Skeletal muscle abnormalities	Dysfunction in skeletal muscles involved in voluntary control of the GI tract, such as pelvic floor muscles and the external anal sphincter, can cause fecal incontinence and difficulty with bowel movements. Weak abdominal muscles can hinder effective stool pushing during defecation. Weak masticatory muscles can lead to difficulty chewing and swallowing
Smooth muscle innervation and neuromuscular transmission	Genetic mutations can affect smooth muscle innervation and disrupt neuromuscular transmission in the enteric nervous system, leading to dysregulation of smooth muscle activity and symptoms such as diarrhea or constipation
Abnormal regulatory pathways	Disruption of neurotransmitters, hormones, and signaling pathways that regulate smooth muscle cells in the GI tract can result in abnormal smooth muscle contraction and relaxation patterns, contributing to GI symptoms
Systemic manifestations	Genetic myopathies can be associated with systemic abnormalities, such as metabolic disturbances and endocrine dysfunction, which indirectly impact the GI tract and contribute to GI symptoms, including impaired gut motility and nutrient absorption
Malabsorption	Chronic GI problems in genetic myopathies can lead to malabsorption of essential nutrients, resulting in deficiencies of vitamins, minerals, and electrolytes, which further impact overall health and exacerbate symptoms

GI: Gastrointestinal.

exacerbating some symptoms[125]. It is important to note that the specific mechanisms of GI involvement can vary depending on the type and subtype of genetic myopathy. Different genetic mutations can lead to distinct pathophysiological processes, resulting in varying GI manifestations[117]. The mechanism of GI manifestations in genetic myopathies involves complex interactions between genetic factors, smooth muscle dysfunction, neuromuscular abnormalities, and dysregulation of regulatory pathways within the GI tract[126]. Understanding these mechanisms is crucial for developing targeted therapies aimed at improving GI function and quality of life in individuals with genetic myopathies.

Genetic and environmental modifiers of GI symptoms in genetic myopathies

GI symptoms in genetic myopathies exhibit significant variability among patients, even individuals with the same genetic

mutation. This variability suggests that additional genetic modifiers, environmental factors, and lifestyle influences play a critical role in shaping the severity and presentation of GI manifestations. Understanding these modifiers is essential for developing personalized treatment strategies and improving patient outcomes (Table 6)[127].

Genetic modifiers and their role in GI dysfunction

Several genetic factors beyond the primary causative mutation influence the severity and progression of GI symptoms in genetic myopathies: Some patients with DMD exhibit severe esophageal dysmotility and gastroparesis, while others have milder symptoms. This variation may be attributed to modifier genes influencing smooth muscle integrity and neuromuscular transmission in the gut[15]. For example, variations in the *laminin alpha 2-chain* gene (which encodes laminin alpha 2, a component of the extracellular matrix) have been implicated in modifying the progression of gut dysmotility in muscular dystrophies[128]. Mitochondrial myopathies are often associated with GI dysmotility, pseudo-obstruction, and malabsorption. The severity of these symptoms is influenced by mtDNA mutations and nuclear-encoded mitochondrial proteins. Patients with heteroplasmic mtDNA mutations may have variable mitochondrial dysfunction, impacting energy-dependent processes such as intestinal peristalsis, secretion, and nutrient absorption[129]. Epigenetic changes, such as DNA methylation and histone modifications, may alter gene expression related to gut motility and inflammation. For instance, maternal diet and early-life exposures can modify the expression of neuromuscular genes regulating gut function, potentially exacerbating symptoms in genetically predisposed individuals[130].

Environmental and lifestyle modifiers

Beyond genetic factors, environmental influences, diet, microbiome composition, and lifestyle factors significantly impact the GI manifestations of genetic myopathies.

The gut microbiota plays a critical role in regulating intestinal motility, immune responses, and metabolism[131]. Patients with genetic myopathies often exhibit gut dysbiosis, characterized by an imbalance in protective vs. pathogenic bacteria, which can exacerbate GI symptoms such as constipation, diarrhea, and bloating. Alterations in the microbiota composition in mitochondrial disorders may further impact energy metabolism, leading to intestinal inflammation and motility disturbances[132].

Protein intake influences muscle function, including smooth muscles in the GI tract. A deficient or imbalanced diet can worsen esophageal dysmotility and delayed gastric emptying. High-fat diets have been associated with increased GI symptoms in patients with metabolic myopathies, whereas fiber-rich diets may enhance motility and reduce constipation. Vitamin deficiencies, particularly B_{12}, D, and magnesium, can contribute to neuromuscular dysfunction, exacerbating gut dysmotility[133]. Reduced mobility due to progressive muscle weakness in genetic myopathies can slow intestinal transit, increasing the risk of severe constipation, pseudo-obstruction, and reflux disease. Patients with DMD or BMD who remain ambulatory for longer durations tend to have less severe GI dysfunction compared to those who become non-ambulatory earlier[134].

Many medications used to manage genetic myopathies, such as steroids, anticonvulsants, and muscle relaxants, can significantly impact gut function. Chronic corticosteroid use in patients with DMD may predispose them to gastroesophageal reflux, delayed gastric emptying, and dysbiosis. Pain medications such as opioids, often prescribed for neuromuscular pain management, can further worsen constipation and reduce gut motility[135]. Emotional stress and anxiety have been linked to worsening gut symptoms in myopathies, particularly in conditions such as DM, where autonomic dysfunction contributes to bowel dysmotility. Access to healthcare and nutritional support varies across populations, affecting early intervention and symptom management and leading to disparities in disease progression [136].

Recognizing the role of genetic and environmental modifiers in GI manifestations of genetic myopathies has important implications for personalized treatment approaches. Identifying genetic modifiers may allow for the development of targeted therapies to modulate gut function in specific patient populations. Probiotics and fecal microbiota transplantation may potentially correct gut dysbiosis and alleviate GI symptoms[137]. Personalized nutritional interventions can improve gut motility and reduce disease burden in genetically predisposed individuals. Understanding how genetic variations influence medication response may help optimize drug therapy for GI symptoms, minimizing side effects while improving motility and digestion.

GI manifestations in genetic myopathies

While the hallmark features of genetic myopathies primarily involve skeletal muscle impairment, it's increasingly recognized that the GI tract can also be affected by these conditions. GI manifestations in genetic myopathies encompass a spectrum of symptoms affecting the digestive system, often accompanying primary muscle weakness and dysfunction. Histological studies of the smooth muscles showed edema, atrophy, and fibrosis of smooth muscles involving the distal esophagus, stomach, and small and large intestines[118]. The specific GI symptoms can differ greatly depending on the type of genetic myopathy and can also vary from person to person, even if they have the same condition.

DMD

GI manifestations are increasingly recognized in DMD. While the primary symptoms of DMD involve skeletal muscle dysfunction, GI involvement can occur and significantly impact patients' quality of life. The GI manifestations usually occur in the second decade of life due to atrophy and degeneration of the smooth muscle layers with connective tissue infiltration[25]. Various GI manifestations can impact digestion, absorption, and waste elimination. Chewing difficulties could be observed in patients with DMD, making it difficult to properly break down food properly, hindering digestion, and potentially leading to malnutrition[134].

Table 6 Genetic and environmental modifiers of gastrointestinal symptoms in genetic myopathies

Modifier type	Key influences	Impact on GI symptoms	Clinical implications
Genetic modifiers	Modifier genes (*e.g.*, *laminin alpha 2-chain gene*, *Lamin A/C*, *Calpain 3*, *Dysferlin*)	Alters smooth muscle integrity and neuromuscular transmission in the gut	Genetic screening may help predict GI severity and guide therapy
	MtDNA mutations (mtDNA heteroplasmy)	Variable energy deficits affecting intestinal motility and absorption	Mitochondrial-targeted therapies and dietary modifications
	Epigenetic changes (DNA methylation, histone modifications)	May regulate neuromuscular gene expression, impacting gut function	Potential target for gene modulation therapy
Gut microbiota	Dysbiosis (loss of beneficial bacteria, increase in pathogenic bacteria)	Worsens constipation, diarrhea, bloating, and inflammation	Probiotics, microbiome-targeted interventions (*e.g.*, fecal microbiota transplantation)
Nutritional status	Protein intake, fiber intake, vitamin deficiencies (*e.g.*, B_{12}, D, Mg)	Deficiencies impair gut motility and neuromuscular coordination	Tailored dietary interventions, vitamin supplementation
Mobility status	Reduced physical activity due to progressive muscle weakness	Slows intestinal transit, leading to severe constipation and GERD	Early physiotherapy and bowel training programs
Medications	Corticosteroids (*e.g.*, used in Duchenne muscular dystrophy), opioids, anticonvulsants	GERD, delayed gastric emptying, constipation	Medication adjustments and use of gut motility agents
Environmental and psychosocial factors	Stress, anxiety, healthcare access disparities	Can worsen functional gut disorders (*e.g.*, IBS-like symptoms in myopathies)	Psychological support and patient education

GERD: Gastroesophageal reflux disease; GI: Gastrointestinal; MtDNA: Mitochondrial DNA.

Dysphagia is the most frequently reported GI symptom observed in patients with DMD due to impaired pharyngeal and oesophageal functions caused by dystrophin deficiency and weakness in the muscles responsible for chewing and swallowing. This can lead to problems with oral intake, including choking, coughing, and aspiration of food or liquids into the airway[34]. GERD, with difficulty emptying the stomach, is prevalent in patients with DMD due to weak smooth muscle tone in the lower esophageal sphincter. The flow of gastric acid back into the esophagus causes symptoms like heartburn, regurgitation, and difficulty swallowing. Barohn *et al*[26] found a significant delay in gastric-emptying times in patients with DMD using radionuclide scintigraphy studies. Gastroparesis with delayed stomach emptying may occur due to impaired smooth muscle function in the gastric wall. This can lead to symptoms such as early satiety, bloating, nausea, vomiting, and abdominal discomfort. Acute gastric dilatation was also reported in patients with DMD[137]. Elevated hepatic transaminases were observed in some children with DMD. Therefore, many authors suggest that unexplained elevated liver transaminases could help early diagnosis of muscular dystrophies[138,139]. Liver steatosis and non-alcoholic fatty liver disease are observed in some patients[140]. Weakening abdominal muscles can hinder the effectiveness of pushing stool during defecation, contributing to constipation. Constipation, fecal impaction, and intestinal pseudo-obstruction may also occur due to dysregulated smooth muscle contractions in the intestines. Kraus *et al*[19] showed that functional constipation is present in 46.7% of patients with DMD, regardless of age or functional status. Weakness in the muscles responsible for maintaining bowel control, such as the external anal sphincter, can result in fecal incontinence. This can lead to involuntary leakage of stool and difficulties in controlling bowel movements[140]. GI manifestations in DMD, such as dysphagia, can lead to inadequate oral intake and difficulties in maintaining a balanced diet. This can result in malnutrition and growth failure, affecting overall health and development. Additionally, dietary factors, reduced physical activity, and medication side effects can exacerbate GI symptoms in individuals with DMD.

However, Lo Cascio et al[18] found a markedly disturbed GI motor function even without GI manifestations. They recommended testing GI motility functions to ensure adequate intestinal transport to prevent potentially life-threatening constipation, especially in older patients with DMD[18]. In addition, Nart *et al*[20] described a series of patients with DMD who presented with severe colonic pseudo-obstruction or volvulus affecting sigmoid that needed urgent intervention. The presence of GI manifestations can also predict impairment of respiratory functions in patients with DMD. Lee *et al*[23] found that constipation is correlated with maximal expiratory pressure; swallowing difficulty is correlated with maximal insufflation capacity, assisted peak cough flow, maximal inspiratory pressure, and maximal expiratory pressure; and mastication difficulty was correlated with forced vital capacity, peak cough flow, assisted peak cough flow, maximal inspiratory pressure, and maximal expiratory pressure. In one study of the cause of Death in the Swedish Registry in patients with DMD, by Wahlgren *et al*[141] showed that GI complications are the cause of death in 1.0/1000 person/year in patients with DMD to be the 3rd cause of death in these patients after cardiopulmonary complications and injury-related pulmonary embolism[141].

BMD

As BMD is a less severe related condition to DMD, characterized by less progressive muscle weakness and degeneration than observed in DMD, the patients usually developed milder and later onset GI manifestations than that observed with DMD. Common GI manifestations include dysphagia, GEED, gastroparesis, abdominal pain, constipation, and fecal

Incontinence. Bianchi *et al*[142] described two brothers with BMD who developed heart failure and various GI symptoms, including dysphagia, post-prandial abdominal pain, constipation, nausea and vomiting, and intestinal pseudo-obstruction. The abdominal pain arises initially after ingesting large amounts of food, progresses to be frequent, and occurs after normal meals[142]. However, Borrelli *et al*[24] studied gastric emptying time in children with DMD and BMD. They found markedly delayed gastric emptying time in these children than in the controls, and children with DMD had longer gastric emptying time than children with BMD[24].

Boys and young men affected with BMD may present with an asymptomatic increase in liver enzyme levels assayed for other reasons, sometimes accurately diagnosed only after extensive GI workouts[21]. Some patients with BMD may also present with non-alcoholic fatty liver disease due to a combination of factors. These include reduced mobility and physical activity resulting from muscle weakness and degeneration, which can lead to weight gain and metabolic disturbances. Metabolic abnormalities inherent to these conditions, such as insulin resistance and dyslipidemia, further contribute to NAFLD development. Additionally, long-term use of glucocorticoid medications, commonly prescribed to improve muscle function, may exacerbate metabolic complications[140,143]. Malnutrition and weight loss could also be observed in BMD, like that observed in DMD, but with later onset and when severely complicated with respiratory failure[144].

LGMD

There is very scarce data about GI manifestations associated with LGMD. Although GI manifestations are not typically a primary feature of LGMD, they can significantly impact affected individuals. These include swallowing difficulties (dysphagia), GERD, nutritional challenges, constipation, and medication-related side effects. These issues stem from muscle weakness and immobility associated with LGMD. The LGMD-associated GI manifestations are not universal and may vary depending on the specific subtype. In LGMD2B, GI symptoms such as dysphagia (difficulty swallowing), gastroesophageal reflux, and elevated liver enzymes have been reported in some patients[27,145,146]. Dysphagia can occur due to weakness in the muscles involved in swallowing, including those in the throat and esophagus[12]. While GI symptoms are less commonly reported in LGMD2C compared to LGMD2B, some patients may experience dysphagia or other GI issues due to muscle weakness[43,147].

Congenital myopathies

Congenital myopathy is a condition characterized by early-onset muscle weakness accompanied by low muscle bulk and tone. Although these symptoms usually appear in neonates and infants, they can also be present in children or adults with milder forms of the condition[51]. Patients suffering from congenital myopathies often face challenges in managing their oral secretions during their neonatal and childhood stages due to excessive salivation and/or poor oral motor control. This excessive salivation can lead to pulmonary complications like aspiration and can have significant negative social impacts[148]. Infants and children who have congenital myopathies often experience difficulties with feeding and swallowing[149]. These difficulties can significantly impact their overall health, including their growth, pulmonary function, oral health, energy levels, and activity levels. Children with nemaline myopathy commonly experience feeding issues during their first year of life, but these tend to improve as they age. Additionally, children with congenital myopathies may experience lower facial weakness, poor oral hygiene, dental care, malocclusion, high-arched palate, jaw contractures, gastroesophageal reflux problems, such as chest or upper abdominal pain, vomiting, aspiration, and recurrent respiratory infections. Constipation and failure to thrive are also common issues they may face[150]. Other less common GI manifestations include diarrhea, incontinence, pyloric stenosis, cholestatis/cholelithiasis, and GI bleeding [151]. Yoo *et al*[28] showed that even in the presence of severe dysphagia and oral motor dysfunction which requires tube feeding for months in neonates with nemaline myopathy, it is possible to obtain sufficient nutrition with an oral diet through a series of dysphagia rehabilitation therapy.

Metabolic myopathies

Metabolic myopathies occur due to missing or deficient enzymes in the energy production process. Some people may not experience any symptoms, while others may have fatigue, exercise intolerance, muscle cramping, and heart or respiratory problems[55]. In severe cases, rhabdomyolysis can develop, leading to kidney damage and failure. This condition can be triggered by various factors such as strenuous exercise, illness, stress, exposure to cold temperatures, or prolonged fasting. While these conditions primarily affect skeletal muscle function, GI manifestations are increasingly recognized as important clinical features[53,152]. GI manifestations in metabolic myopathies are diverse, depending on the specific disorder and underlying metabolic abnormalities. Common symptoms include recurrent abdominal pain, often associated with metabolic disturbances or rhabdomyolysis episodes[54]. Metabolic disruptions can affect gastric motility and emptying, leading to nausea and vomiting. Dysregulation of intestinal motility may result in diarrhea or constipation, causing GI discomfort[142]. Certain metabolic myopathies may increase the risk of GERD due to impaired esophageal or gastric motility. Additionally, weakness or dysfunction of oropharyngeal and esophageal muscles can lead to dysphagia, posing a risk of aspiration[12].

In Glycogen storage disease type I, patients may experience intermittent diarrhea, which appears to worsen with age. The exact cause is unclear, possibly due to inflammation related to disturbed neutrophil function commonly observed in Glycogenosis type IB (GSD IB), as evidenced by high fecal calprotectin[153,154]. GSD IB can also cause a Crohn's disease-like inflammatory bowel disease (IBD) that can significantly impair a patient's quality of life[155]. Medium-chain acyl-CoA dehydrogenase deficiency deficiency usually occurs in infants or young children and may result in vomiting, lethargy, and hypoglycemia which may progress to coma[156]. Carnitine deficiency may be a cause of GI dysmotility, with recurrent episodes of abdominal pain and diarrhea. It also may present with fulminant liver failure and presentation

like that in Reye syndrome[157]. Hepatomegaly may also be one of the manifestations of GSDs and neutral lipid storage disease[158]. Patients with neutral lipid storage disease may also present with liver steatosis, hepatosplenomegaly, and even liver cirrhosis[159]. Wolman disease is a rare autosomal-recessive disease caused by a lysosomal acid lipase deficiency. Infants suffering from this disease may present with GI symptoms such as diarrhea, vomiting, feeding difficulties, hepatosplenomegaly, failure to thrive, stunted growth, and calcifications in the adrenal glands[160].

Danon disease is a rare genetic X-linked lysosomal storage disorder that affects males and is caused by mutations in the *LAMP2* gene. This disorder causes a build-up of glycogen and autophagic debris in the tissues, particularly in the cardiac and skeletal muscles[161]. Individuals affected by Danon disease may experience a variety of symptoms, including GI problems, breathing difficulties, and visual abnormalities. Some of the GI symptoms that may occur include difficulty swallowing, GERD, abdominal pain, diarrhea, and constipation. Many affected males may also experience liver enlargement and elevated liver enzymes, which may be due to skeletal muscle damage rather than liver dysfunction[162].

Mitochondrial myopathies

Mitochondrial myopathies are a group of disorders characterized by dysfunctional mitochondria, the energy-producing organelles in cells. While these disorders primarily affect skeletal muscles, they can also involve various other organs, including the GI system[63]. GI manifestations are common in mitochondrial myopathies, reflecting the systemic nature of these disorders. Patients with mitochondrial myopathies often experience dysphagia, GERD, and gastroparesis due to impaired muscle function in the esophagus and stomach. Additionally, dysregulation of intestinal motility can lead to diarrhea, constipation, abdominal pain, GI pseudo-obstruction, pancreatitis with/without diabetes and with/without exocrine pancreas insufficiency, and hepatopathy. Malabsorption of nutrients, pancreatic dysfunction, and liver involvement may further exacerbate GI symptoms[163-165].

Mitochondrial neuro-GI encephalopathy (MNGIE) is the most well-known mitochondrial disorder involving the GI tract. It causes dysphagia, achalasia, GERD, vomiting, especially at night, Pancreatitis, hepatopathy, steatosis, Pseudo-obstruction, megacolon, and diarrhea[166]. MELAS is a mitochondrial disorder that causes recurrent stroke-like episodes, seizures, and muscle weakness. One of the main symptoms of MELAS is cyclic or episodic vomiting, which can sometimes be mistaken for bulimia due to its intensity[167]. Migraine is also common in patients with MELAS and can cause vomiting as well. However, administering phenytoin to MELAS patients may trigger intestinal pseudo-obstruction [168]. Additionally, diarrhea may occur due to GI dysmotility or pancreatic insufficiency. Occasionally, patients with MELAS may present in the acute surgical abdomen[169]. Patients with MNGIE may be easily satiated and nauseated and may have an increased bowel frequency or intermittent diarrhea[32].

Leigh syndrome, also known as subacute necrotizing encephalomyelopathy, is a severe neurological disorder caused by mitochondria dysfunction. It typically appears in infancy and can cause muscle weakness and movement disorders. Patients may also experience GI issues such as dysphagia, vomiting, and diarrhea, which are likely due to damage in the brainstem's swallowing center. These issues can further decrease the patient's nutrition intake, leading to malnutrition or failure to thrive[170]. In cases of Kearns-Sayre syndrome, around 15% of patients may experience dysphagia due to primary esophageal dysmotility, neurogenic causes, or a combination of factors[33]. Patients with this syndrome may also have a near absence of pharyngeal peristalsis, abnormally low upper esophageal sphincter resting pressure, and an absence of proximal esophageal peristalsis[171].

MD

DM, particularly DM1 and DM2, presents with a variety of GI manifestations due to the multisystem nature of the disease. GI manifestations occur in about 50% of patients, especially in DM1, and may occur at any level and affect various parts of the GI tract. The onset of GI manifestation may even precede the musculoskeletal features and may be the first sign of dystrophic disease. However, these manifestations could develop gradually, so the patient is unaware of the exact onset and has little awareness of symptoms[118]. Common GI symptoms include asymmetric pharyngeal contraction, dysphagia, dyspepsia, heartburn, regurgitation, GERD, and gastroparesis, which can lead to symptoms like early satiety, bloating, nausea, vomiting, and abdominal discomfort[172]. These manifestations are due to pathological atrophic abnormalities of striated pharyngeal, esophageal, and gastric muscles[11,31]. Radiological, manometric, and ultrasonographic evidence reveal reduced peristaltic activity, delayed gastric emptying, and visceral dilatation, contributing to symptoms like gastroparesis[173,174]. Moreover, studies highlight abnormalities in small intestine motility, with reports of low-amplitude contractions and myotonic phenomena[175].

Diarrhea, often accompanied by malabsorption, steatorrhea, and abdominal cramps, is a common complaint among MD patients. Additionally, paralytic ileus has been documented. The abdominal pain associated with MD can occur in any part of the abdomen without specific characteristics or triggers. Episodic diarrhea, present in up to 33% of cases, is particularly debilitating and can significantly impact a patient's social life, especially when compounded with anal incontinence. Diarrhea is a common complaint among patients with DM, often accompanied by malabsorption, steatorrhea, and abdominal cramps. In addition, paralytic ileus has been documented[176]. The abdominal pain associated with DM can occur in any part of the abdomen without specific characteristics or triggers. Episodic diarrhea, present in about one-third of cases, is particularly debilitating and can significantly impact a patient's social life, especially when compounded with anal incontinence[177]. Constipation, often associated with dyschezia and fecal incontinence, are other common features frequently attributed to weakened abdominal muscles and dysregulated intestinal motility, which makes it difficult to pass stool and alterations in resting and squeezing pressures[29]. It could also occur secondary to hypothyroidism, which is also common in DM[178]. Megacolon, sigmoid volvulus, and segmental narrowing indicate significant motility disturbances[30]. Histologic studies suggest muscular abnormalities, with findings of atrophy, fibrosis, and cellular changes in the anal sphincter. Dystrophy and fatty infiltration of the smooth fibers of the stomach, small bowel, and colon have been described[31]. Peristaltic abnormalities can be documented radiologically.

Hilbert *et al*[16] conducted a study revealing GI manifestations in both DM1 and DM2. They observed that individuals with DM1 and DM2 had a higher likelihood of getting cholecystectomy at a younger age compared to the control group. The study also found that higher body mass index and longer disease duration were associated with a greater risk of GI manifestations in DM1. At the same time, female sex was a risk factor in DM2[16].

Diagnostic approaches of GI manifestations in genetic myopathies

Diagnostic approaches for evaluating GI manifestations in genetic myopathies aim to identify the underlying causes of symptoms, evaluate their severities, and guide appropriate management strategies (Figure 2)[179]. These approaches typically involve a combination of clinical evaluation, imaging studies, physiological tests, histological analysis, and genetic testing. Clinical evaluation is the initial step in this approach. A detailed patient history should involve inquiry about different GI symptoms such as dysphagia, reflux, abdominal pain, constipation, diarrhea, and fecal incontinence, together with documenting the onset, duration, severity, and progression of symptoms[177]. Then, a thorough physical examination, including assessment of muscle strength, tone, and bulk, should be performed, paying attention to signs of muscle weakness, atrophy, or contractures, as well as abdominal tenderness or distention and peri-anal area[180].

Imaging studies are frequently needed to evaluate the degree of GI involvement in various types of myopathies. Abdominal X-rays can help detect signs of intestinal obstruction, megacolon, volvulus, or other structural abnormalities [181]. Abdominal ultrasound is useful for assessing liver size, detecting hepatomegaly or fatty liver changes, and evaluating gallbladder abnormalities. Upper GI series with barium swallow and small bowel follow-through can assess for esophageal dysmotility, gastroesophageal reflux, gastric emptying abnormalities, and small bowel transit time[121]. Radiological evaluation of colon transit time can help assess patients with constipation and other colonic or rectal impairments[182].

While CT and MRI are both used to evaluate GI anatomy and complications such as volvulus or intussusception, MRI offers distinct advantages over CT in several key areas. MRI provides superior soft tissue contrast, allowing for detailed visualization of muscle atrophy, fibrosis, and inflammation in the GI tract[183]. It is particularly beneficial for assessing intestinal pseudo-obstruction, gastroparesis, and dysphagia, which are common in DMD, DM, and mitochondrial myopathies[184]. Additionally, MRI enables cine imaging, which allows for real-time assessment of gastric and intestinal motility, helping distinguish true mechanical obstruction from functional dysmotility—a crucial factor in surgical *vs* medical management decisions[185]. Another major advantage of MRI is its ability to detect hepatic and pancreatic involvement, particularly in metabolic myopathies, where MRI can quantify hepatic steatosis in conditions such as mitochondrial myopathies and GSDs, guiding early dietary and hepatoprotective interventions. Furthermore, MRI does not expose patients to ionizing radiation, making it a safer option for pediatric patients and those requiring serial imaging [186].

On the other hand, CT remains valuable in acute settings, particularly for detecting intestinal obstruction, perforation, ischemia, and GI bleeding, conditions that may necessitate urgent surgical intervention. CT's rapid acquisition time and widespread availability make it the preferred first-line imaging modality in emergencies[187]. Additionally, CT angiography can be used to evaluate vascular complications, which may be present in mitochondrial disorders. However, CT's reliance on ionizing radiation makes it less suitable for repeated imaging, particularly in children. While MRI is superior for functional and soft tissue assessments, CT is often preferred for evaluating acute structural abnormalities and life-threatening GI emergencies[188]. In clinical practice, these two imaging techniques are complementary, with MRI being the preferred choice for chronic, functional, and metabolic evaluations. In contrast, CT is more suited for acute, structural, and emergency assessments. By integrating both modalities, clinicians can comprehensively understand GI involvement in genetic myopathies, optimizing diagnostic accuracy and guiding appropriate management strategies (Table 7)[17].

Various physiological tests may also be needed. Esophageal manometry can measure esophageal motility and pressure dynamics, helping diagnose disorders such as achalasia, esophageal spasm, or ineffective oesophageal peristalsis[189]. Ambulatory pH monitoring evaluates esophageal acid exposure over time, helping diagnose GERD and assess treatment efficacy[190]. GI motility studies, such as esophageal transit studies or colonic transit studies, can assess the coordination and function of the GI tract, aiding in the diagnosis of dysmotility disorders[172]. Gastric Emptying evaluation is needed to evaluate gastroparesis. Radionuclide or scintigraphy studies assess gastric emptying times, aiding in diagnosing gastroparesis or delayed gastric emptying[191]. Anorectal manometry evaluates anal sphincter function, rectal sensation, and recto-anal reflexes, assisting in the diagnosis of fecal incontinence, constipation, or pelvic floor dysfunction[192].

Histological analysis could occasionally be helpful. Endoscopic evaluation with mucosal biopsy may be performed to assess for histological changes in the GI tract, such as inflammation, fibrosis, or smooth muscle abnormalities[193]. This can be particularly useful in diagnosing conditions like eosinophilic esophagitis or IBD. In cases where GI smooth muscle involvement is suspected, such as in certain genetic myopathies, a muscle biopsy may be indicated to evaluate for histological abnormalities, including muscle atrophy, fibrosis, or lipid accumulation[194].

Genetic testing can evaluate the exact type of myopathy and the presence of any syndromic myopathies. Genetic testing using NGS panels can identify pathogenic mutations associated with various genetic myopathies, including DMD, BMD, LGMD, congenital myopathies, metabolic myopathies, mitochondrial myopathies, and DM[195]. Targeted sequencing may be performed for specific genes implicated in GI motility disorders or metabolic myopathies, depending on the clinical presentation and suspected underlying condition[54]. Given the multisystem nature of many genetic myopathies, a multidisciplinary approach involving gastroenterologists, neurologists, geneticists, and other specialists may be necessary to evaluate and manage GI manifestations comprehensively.

Impact of GI symptoms on quality of life and daily functioning

GI symptoms are a significant yet often overlooked component of genetic myopathies, profoundly affecting nutrition, daily activities, social interactions, and mental well-being. While much of the clinical focus in genetic myopathies is on

Table 7 Comparison between magnetic resonance imaging and computed tomography in gastrointestinal myopathies

Feature	MRI	Computed tomography
Tissue contrast	Superior soft tissue contrast; excellent for detecting muscle atrophy, fibrosis, and inflammation	Moderate contrast; better for bony structures and acute bleeding
Radiation exposure	No ionizing radiation—safer for children and repeated follow-ups	Uses ionizing radiation, which may be concerning for pediatric patients and those needing serial imaging
Visualization of smooth muscle	More detailed assessment of intestinal wall abnormalities, fibrosis, and motility issues	Less sensitive in detecting smooth muscle pathology
Gastric and intestinal motility	MRI can provide cine imaging for real-time assessment of gastric emptying and intestinal movement	Lacks dynamic imaging capability for motility disorders
Bowel obstruction and pseudo-obstruction	Can differentiate between true obstruction *vs* pseudo-obstruction based on bowel wall motion	Effective for detecting acute bowel obstructions but lacks functional assessment
Detection of liver and pancreatic involvement	Better visualization of hepatic and pancreatic steatosis, common in metabolic myopathies	Good for detecting structural abnormalities, such as tumors or calcifications
Practical limitations	Longer scan time, requires patient cooperation, contraindicated in patients with metal implants	Quick scan time, widely available, useful for emergency settings

MRI: Magnetic resonance imaging.

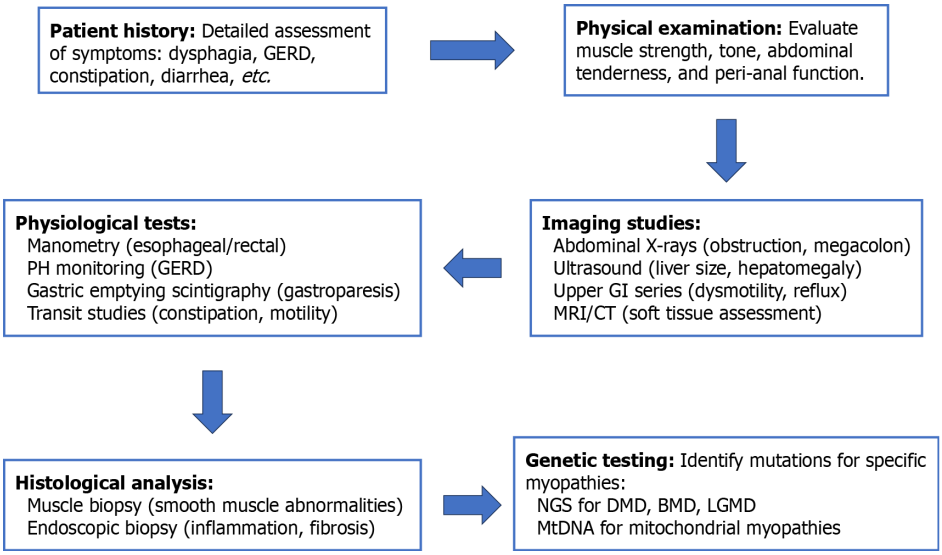


Figure 2 Diagnostic approaches for gastrointestinal manifestations in genetic myopathies. CT: Computed tomography; BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy; GERD: Gastroesophageal reflux disease; GI: Gastrointestinal; LGMD: Limb-girdle muscular dystrophy; MRI: Magnetic resonance imaging; MtDNA: Mitochondrial DNA; NGS: Next-generation sequencing.

muscle weakness and mobility impairment, dysphagia, GERD, constipation, gastroparesis, and intestinal pseudo-obstruction impose additional burdens, leading to malnutrition, dehydration, chronic pain, and reduced independence [196]. The cumulative effects of these GI complications significantly impact the quality of life, necessitating a multidisciplinary approach to management.

One of the most critical consequences of GI dysfunction in genetic myopathies is malnutrition, which results from poor oral intake, impaired digestion, and inefficient nutrient absorption. Dysphagia (swallowing difficulties) and esophageal dysmotility, common in conditions like DMD, DM1, and mitochondrial myopathies, lead to reduced calorie and protein intake, exacerbating muscle atrophy, fatigue, and immune dysfunction[197]. Additionally, gastroparesis (delayed gastric emptying) results in early satiety, nausea, and bloating, making it difficult for patients to consume adequate nutrition. Over time, malnutrition worsens disease progression, delays wound healing, and weakens the immune system, increasing susceptibility to infections[173]. The resulting malnutrition impacts the child's daily functioning as reduced energy levels due to muscle wasting impair mobility and functional independence. In addition, nutritional deficiencies often lead to frequent hospital admissions for hydration and feeding support. Furthermore, severe dysphagia may necessitate gastrostomy tube (G-tube) placement, impacting eating habits and social participation[198,199].

GERD and esophageal dysmotility are prevalent in BMD, LGMD, and mitochondrial myopathies, leading to chronic acid reflux, heartburn, and regurgitation. Frequent aspiration events can result in recurrent pneumonia and worsening respiratory function, particularly in non-ambulatory patients. Chronic epigastric pain and discomfort further reduce

appetite, disrupt sleep, and impair overall well-being[200]. Nocturnal reflux causes sleep disturbances, leading to daytime fatigue and cognitive difficulties. Patients may avoid eating in public due to reflux-related discomfort and coughing. Chronic GERD often necessitates long-term PPIs and dietary restrictions, adding to the treatment burden[201].

Chronic constipation, slow colonic transit, and intestinal pseudo-obstruction are significant issues in DMD, mitochondrial myopathies, and DM, resulting from weakened smooth muscle contraction and autonomic dysfunction. Patients experience severe abdominal pain, bloating, nausea, and incomplete bowel movements, leading to emotional distress and decreased daily productivity[178]. Additionally, some patients suffer from fecal incontinence, which significantly affects self-esteem and social participation. Frequent episodes of abdominal pain and unpredictable bowel movements make it difficult for patients to maintain school attendance or employment. Fear of accidents in public settings can lead to social isolation and anxiety. Patients often require assistance with toileting and bowel management programs, impacting both their autonomy and caregiver burden[202].

GI symptoms in genetic myopathies not only affect physical health but also lead to significant emotional and social burdens. Anxiety, depression, and reduced self-esteem are common among patients experiencing chronic pain, dietary restrictions, and unpredictable bowel habits. The need for feeding tubes, dietary modifications, and bowel programs can make patients feel different from their peers, leading to withdrawal from social activities[203]. Chronic illness and social embarrassment from GI symptoms contribute to mental health issues. Patients may avoid eating in restaurants or attending events due to dietary restrictions or bathroom concerns. The need for specialized diets, feeding assistance, and frequent medical visits places financial strain on families and increases caregiver fatigue[204]. GI symptoms in genetic myopathies lead to a vicious cycle of malnutrition, chronic pain, emotional distress, and reduced independence. The cumulative effects significantly diminish patients' overall quality of life and daily functioning[205]. To address these challenges, multidisciplinary management involving gastroenterologists, dietitians, neurologists, physiotherapists, and mental health professionals is essential.

Management of GI manifestations in genetic myopathies

Managing GI manifestations in genetic myopathies involves a multidisciplinary approach to alleviate symptoms, improve nutritional status, and optimize GI function (Figure 3). Treatment strategies may vary depending on the specific symptoms, underlying genetic disorders, and individual patient needs. Nutritional Support is a cornerstone of managing patients with genetic myopathies, as malnutrition is usually a frequent complication. Implementing dietary adjustments tailored to address specific GI symptoms helps manage many GI disorders[205]. For example, in cases of dysphagia or swallowing difficulties, modify food consistency or texture to facilitate safer swallowing and reduce the risk of aspiration. Oral or enteral nutritional supplements are provided to address malnutrition, weight loss, or deficiencies in essential nutrients. These supplements may include high-calorie formulas, protein supplements, vitamins, and minerals[206].

Management of myopathy-associated GI symptoms aims to improve the patient's quality of life and general well-being. If the patient suffers from dysphagia, implementing swallowing rehabilitation exercises, dietary modifications, and positioning techniques improves swallowing function and reduces the risk of aspiration[207]. Speech-language pathology evaluation and therapy may also be beneficial. In symptomatic GERD, using pharmacological agents such as PPIs, histamine-2 receptor antagonists, or prokinetic agents helps to manage symptoms of GERD and reduce gastric acid secretion. To manage gastroparesis, we need to employ dietary modifications (*e.g.*, small, frequent meals; low-fat diet), prokinetic medications (*e.g.*, metoclopramide, domperidone), antiemetics, and gastric electrical stimulation for refractory cases to improve gastric emptying and alleviate symptoms[208]. As constipation and fecal incontinence are common problems in patients with genetic myopathies, we may need to implement dietary fiber supplementation, osmotic laxatives, stool softeners, bowel management programs, biofeedback therapy, or sacral nerve stimulation to manage constipation and fecal incontinence[209]. To manage abdominal pain, patients can utilize analgesic medications and antispasmodics, modify their diet, practice relaxation techniques, and may need psychological interventions to address these manifestations. At the same time, diarrhea can be controlled by properly identifying and treating underlying causes, such as bacterial overgrowth, malabsorption, or medication side effects. Antidiarrheal agents, dietary modifications, and probiotics may be beneficial[210]. We may need surgical intervention to relieve the myopathy-associated GI manifestations in certain conditions. Fundoplication can be performed in severe GERD, pyloroplasty, gastric bypass for refractory gastroparesis, or fecal diversion procedures can be performed in intractable fecal incontinence. Gastrostomy or jejunostomy feeding tubes may be considered in patients with severe dysphagia, swallowing difficulties, or inadequate oral intake to ensure adequate nutrition and hydration[211].

General rehabilitation and supportive care are other vital cornerstones in managing patients with genetic myopathies. Physical therapy interventions improve or maintain muscle strength, mobility, and functional independence, which may indirectly benefit GI function by enhancing overall physical health[14]. Occupational therapy can address activities of daily living, adaptive equipment needs, and meal preparation and feeding strategies in patients with upper extremity weakness or coordination deficits[212]. Speech-language pathologists can be engaged to assess and manage swallowing disorders, dysphagia, and communication difficulties, providing exercises and strategies to improve swallowing safety and efficiency[213].

Another cornerstone in the management is patient and caregiver education. Patients need to be educated about the nature of their genetic myopathy, associated GI manifestations, and available treatment options. Patients should be empowered to actively participate in their care and advocate for their needs[214]. They also may need psychological support, counseling, and coping strategies to address emotional distress, anxiety, depression, or social isolation associated with chronic GI symptoms and genetic myopathies. Given the genetic nature of genetic myopathies, we must provide genetic counseling to patients and families to discuss inheritance patterns, genetic testing options, recurrence risks, and family planning decisions[215]. We also need to facilitate access to support groups, online communities, or peer networks for individuals and families affected by genetic myopathies, allowing them to share experiences, seek advice,

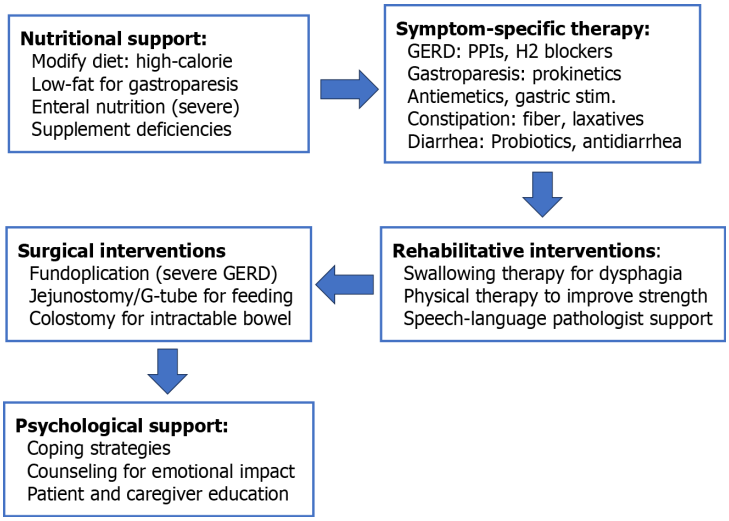


Figure 3 Management strategies for gastrointestinal manifestations in genetic myopathies. GERD: Gastroesophageal reflux disease; PPIs: Proton pump inhibitors.

and receive emotional support[216]. By employing a comprehensive and individualized approach to management, healthcare providers can effectively address GI manifestations in genetic myopathies, improve patients' quality of life, and promote optimal GI health. Regular monitoring and multidisciplinary collaboration are essential for ongoing assessment and adjustment of treatment plans based on patients' evolving needs and responses.

Patients perspectives

Understanding patient perspectives in genetic myopathies is essential for delivering patient-centered care, addressing unique challenges, and improving overall well-being. There are various impacts of GI disorders on patients with genetic myopathies, impacting their daily life, social, and psychological life, expose them to many communication challenges[14]. The impact of GI disorders affects different life aspects of patients with myopathies. Patients with genetic myo-pathies often experience progressive muscle weakness, fatigue, and mobility limitations, impacting their ability to perform activities of daily living independently. Muscle weakness and motor difficulties can affect tasks such as walking, climbing stairs, lifting objects, and maintaining balance, leading to increased dependency on caregivers and assistive devices[217]. Patients may also face challenges with mobility both indoors and outdoors, affecting their ability to navigate their environment, participate in social activities, and access community resources[218].

Living with a genetic myopathy can cause emotional distress, anxiety, depression, frustration, and feelings of isolation due to physical limitations, unpredictable disease progression, and uncertainty about the future. Patients may experience social isolation or withdrawal from social activities due to mobility limitations, communication difficulties, stigma, and barriers to accessibility[219]. Genetic myopathies can strain relationships with family members, friends, and peers, as patients may require increased support, understanding, and accommodations to participate in social interactions and maintain meaningful connections[220]. Some genetic myopathies affect the muscles involved in speech and swallowing, leading to dysarthria, dysphonia, and dysphagia, which can affect communication clarity, fluency, and effectiveness. Therefore, Patients may require assistive communication devices, such as speech-generating devices, communication boards, or alternative augmentative communication systems, to facilitate effective communication and expression of needs and preferences[221].

Maintaining independence and autonomy is a significant concern for patients with genetic myopathies, as they strive to preserve their ability to engage in meaningful activities, make decisions, and manage daily tasks[222]. Patients prioritize factors that enhance their quality of life, such as access to supportive care services, assistive technologies, physical rehabilitation, social support networks, and opportunities for participation and inclusion. Patients value collaborative decision-making processes that involve open communication, mutual respect, and consideration of their preferences, goals, values, and priorities in treatment planning. Patients appreciate personalized and holistic approaches to care that address their unique needs, preferences, and goals, recognizing that one-size-fits-all interventions may not be suitable for everyone[223].

Patients may encounter barriers to accessing healthcare services, including financial constraints, transportation limitations, geographical distance to specialized centers, and insurance coverage issues, impacting their ability to receive timely and comprehensive care[224]. Patients benefit from access to multidisciplinary healthcare teams comprised of specialists in neurology, rehabilitation, genetics, nutrition, psychology, and social work, who collaborate to provide coordinated and integrated care. Patients and their caregivers advocate for their needs, rights, and interests by raising awareness, participating in advocacy initiatives, engaging with patient advocacy organizations, and promoting policy changes to improve access to care, research funding, and social support services[225]. Patients develop self-advocacy skills to communicate their needs effectively, navigate healthcare systems, access resources, and assert their rights as active participants in their care and decision-making processes[226].

Patients can contribute to research efforts by participating in clinical trials, observational studies, patient registries, and patient-reported outcome measures, providing valuable insights into disease progression, treatment outcomes, and quality of life. Patients embrace technological advancements, assistive devices, adaptive technologies, and telehealth solutions that enhance their independence, communication, mobility, and access to healthcare services, fostering innovation and empowerment within the community[227]. By considering patient perspectives in genetic myopathies, healthcare providers can deliver compassionate, patient-centered care that addresses the holistic needs, preferences, and priorities of individuals and their families, ultimately improving their quality of life and well-being. Collaboration between patients, caregivers, healthcare professionals, researchers, and advocacy organizations is essential for promoting positive outcomes and fostering a supportive and inclusive community for individuals living with genetic myopathies.

Future directions and research recommendation

Future directions and research in GI manifestations of genetic myopathies are essential for advancing understanding, improving diagnosis, developing targeted therapies, and enhancing patient care. Further genetic studies, including whole-exome sequencing, genome-wide association studies, and functional genomics approaches, are needed to identify novel genes and variants associated with GI manifestations in genetic myopathies. Research efforts should focus on elucidating GI involvement's molecular mechanisms, including the role of genetic mutations, aberrant signaling pathways, cellular dysfunction, and tissue-specific pathophysiological changes[228].

Research should continue to identify biomarkers, such as circulating biomarkers, genetic markers, imaging biomarkers, and molecular signatures, for early detection, risk stratification, disease monitoring, and treatment response assessment in GI manifestations of genetic myopathies. We also need to develop non-invasive diagnostic tools, including imaging modalities, functional tests, and molecular assays, for assessing GI motility, smooth muscle function, neuromuscular integrity, and tissue pathology in patients with genetic myopathies. We also need to explore targeted therapeutic approaches, including pharmacological interventions, gene therapies, and molecular interventions, aiming to correct underlying molecular defects, modulate signaling pathways, restore muscle function, and improve GI motility and function. Investigating novel treatment modalities, such as gene editing technologies, RNA-based therapies, stem cell therapies, and tissue engineering strategies, could help to address GI manifestations and associated complications in genetic myopathies[229].

Research also could extend to the pathophysiology of enteric neuropathy, neurodegeneration, and dysregulation of the enteric nervous system in genetic myopathies, including the role of neurotransmitters, neural circuits, and neuromodulator pathways in GI motility and function. We also need to explore neuroprotective strategies, neuromodulating interventions, and neural stimulation techniques to preserve enteric nervous system integrity, restore neuronal function, and enhance GI peristalsis and coordination. In addition, there is a need to develop and characterize preclinical models, including animal models, cellular models, organoid cultures, and patient-derived induced pluripotent stem cells, for studying GI manifestations of genetic myopathies, testing therapeutic interventions, and predicting clinical outcomes [230]. It is also important to translate these preclinical findings into clinical applications, including the validation of therapeutic targets, preclinical efficacy studies, early-phase clinical trials, and the implementation of personalized medicine approaches for patients with genetic myopathies affecting the GI tract[231]. We also need to conduct clinical trials to evaluate the safety, efficacy, and tolerability of novel therapeutic interventions, disease-modifying agents, symptomatic treatments, and multidisciplinary care approaches for managing GI manifestations and improving patient outcomes in genetic myopathies. Long-term observational and natural history studies are also required to characterize the progression of GI involvement, identify prognostic factors, assess treatment responses, and evaluate the impact of interventions on disease course, quality of life, and survival[232].

Integrating patient-reported outcomes, patient-centered measures, and quality-of-life assessments into clinical research studies and therapeutic trials helps capture GI manifestations' impact on patient's symptoms, functional status, psychosocial well-being, and overall quality of life[233]. We also should engage patients, caregivers, advocacy organizations, and community stakeholders in research prioritization, study design, recruitment strategies, and dissemination of research findings to ensure that research efforts are patient-centered, relevant, and impactful. It is also vital to establish collaborative research networks, consortia, and multidisciplinary teams comprising clinicians, researchers, industry partners, patient advocates, and regulatory agencies to facilitate data sharing, resource sharing, collaborative research projects, and knowledge exchange in the GI manifestations of genetic myopathies[234]. We should also promote data-sharing initiatives, biobanks, registries, and open-access databases for sharing clinical, genomic, imaging, histopathological, and experimental data to accelerate research progress, foster collaborations, and enhance reproducibility and transparency in research efforts.

Limitations of the study

The review has several limitations that warrant consideration. Firstly, although the review included a substantial number of studies, the overall sample size may still limit the generalizability of findings to broader populations. Additionally, the potential for publication bias exists, as the review may have favored studies reporting positive results, potentially skewing the overall understanding of GI manifestations in genetic myopathies. Moreover, the presence of heterogeneity across included studies, stemming from variations in study designs, patient populations, and methodologies, may affect the synthesis of results and the formation of conclusive interpretations. Furthermore, the quality of evidence across studies varied, which could impact the reliability and validity of the conclusions drawn from the review. The limited availability of data on certain aspects of GI manifestations in genetic myopathies may also restrict the comprehensiveness of the review. Language bias may be present, as only studies published in English were included, potentially excluding relevant research published in other languages. Finally, bias in reporting within the included studies could influence the accuracy of the synthesized findings, affecting the overall robustness of the review's conclusions.

CONCLUSION

In conclusion, GI manifestations in genetic myopathies pose significant diagnostic and management challenges, necessitating a comprehensive and multidisciplinary approach for optimal care. Clinical evaluation, imaging studies, physiological tests, histological analysis, and genetic testing play pivotal roles in identifying underlying causes, assessing severity, and guiding management strategies. Nutritional support, symptomatic management, rehabilitative interventions, and patient education are essential components of managing GI symptoms in genetic myopathies, aiming to improve quality of life and overall well-being. Future research directions should focus on elucidating molecular mechanisms, identifying biomarkers, developing targeted therapies, and enhancing patient-centered care to address the complex interplay of GI manifestations in genetic myopathies effectively. By integrating patient perspectives, advancing scientific knowledge, and fostering collaborative efforts, healthcare providers and researchers can strive towards improving outcomes and enhancing the lives of individuals living with genetic myopathies and associated GI complications.

FOOTNOTES

Author contributions: Al-Beltagi M conceptualized and designed the study, conducted the literature search, and wrote the initial draft of the manuscript; Saeed N contributed to data extraction, quality assessment, and critical revision of the manuscript; Bediwy A assisted in data synthesis, statistical analysis, and manuscript editing; Elbeltagi R contributed to manuscript formatting, reference management, and final proofreading; all authors reviewed and approved the final version of the manuscript.

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SYSTEMATIC REVIEWS

Current state of nutritional psychiatry: A scoping review of randomized controlled trials

Takahiko Nagamine

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Abstract

BACKGROUND

Nutritional psychiatry is a rapidly expanding field of research, with mounting evidence suggesting that nutritional factors may play a role in the development of psychiatric disorders.

AIM

To examine the level of evidence for nutritional psychiatry.

METHODS

A scoping review was conducted to assess the current state of nutritional psychiatry, including a search for randomized controlled trials (RCTs).

RESULTS

The review identified a total of seven papers, with many concentrating on the relationship between depression and the gut microbiome. A salient issue that emerged from this review was the paucity of sample size in many studies. The inherent complexity of nutritional studies, characterized by a multitude of potential factors and exposures that often act as confounders, poses significant challenges to the development of effective RCT designs. The analysis revealed that probiotics, though demonstrating efficacy, exhibited a modest effect size.

CONCLUSION

Conducting RCTs with effective markers is imperative from these studies. The implementation of Mendelian randomization and the investigation of mechanisms in basic research are essential complementary approaches.

Key Words: Nutritional psychiatry; Randomized controlled trial; Mendelian randomization; Fundamental research; Probiotics; Gut microbiota

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Core Tip: The number and quality of randomized controlled trials (RCTs) in the field of nutritional psychiatry remain inadequate. The relationship between nutrition and psychiatric disorders is challenging to demonstrate causally in RCTs due to the multitude of confounding factors and the relatively modest effect sizes observed. To enhance the evidence base in nutritional psychiatry, it would be beneficial to utilize not only RCTs but also data from Mendelian randomization studies and fundamental research, with the aim of elucidating the underlying mechanisms.

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INTRODUCTION

Nutrition psychiatry is a field of scientific inquiry that seeks to understand the impact of dietary and nutritional factors on brain function and mental health[1]. There are several reasons why the field of nutrition psychiatry is receiving increased attention. One factor contributing to the growing interest in nutrition psychiatry is the observed increase in mental illnesses. In recent years, there has been a notable rise in the prevalence of conditions such as depression and anxiety disorders, underscoring the need for a deeper understanding of their underlying causes and the development of novel therapeutic approaches[2]. Second, the relationship between diet and health has attracted attention[3]. It is becoming increasingly clear that diet is deeply involved not only in physical health but also in mental health. Given the brain's capacity for plasticity, whereby it can adapt in response to experience and environment, it is reasonable to posit that dietary factors may exert a beneficial influence on brain function. Nutritional psychiatry encompasses research into a number of different areas including neurotransmitters, gut microbiota, and inflammation[4]. Neurotransmitters such as serotonin, dopamine, and norepinephrine play a pivotal role in emotional regulation and motivation[5]. Dietary modifications can influence the synthesis and secretion of these neurotransmitters, thereby impacting mental state. Gut microbiota is not only involved in the synthesis of neurotransmitters such as serotonin and dopamine, but also affects mental state through the gut-brain axis. It has been demonstrated that chronic inflammation increases the risk of developing mental illnesses such as depression and anxiety disorders[6]. In addition, dietary therapy has been shown to have the effect of suppressing inflammatory responses[7]. However, nutritional psychiatry is a relatively new field, and the evidence base supporting its claims has yet to be fully established. The relationship between nutrients and mental function is primarily based on observational studies, which may be subject to bias.

Therefore, the present paper provides a review of the currently available randomized controlled trials (RCTs) in the field of nutritional psychiatry, which have a higher level of evidence than observational studies, and provides suggestions for future research methods.

MATERIALS AND METHODS

A comprehensive electronic search of the PubMed and J-STAGE databases was conducted for articles published in English up to December 2024. The search terms employed were "nutritional psychiatry," "randomized controlled trial," "gut microbiota," and "mental function." The abstracts of the retrieved articles were reviewed, and only those that described either diet, probiotics, or nutrients were included in the subsequent analysis. The screening and selection process was conducted by the author. A flow diagram illustrating the review process, including details of the databases and registers searched, is presented in Figure 1.

RESULTS

A preliminary evaluation of 76 abstracts revealed that only a small number of studies met the criteria of the present study. The preponderance of studies in the domain of nutritional psychiatry were of an observational or case report nature, with a modest number classified as RCTs. The screening process identified 13 RCTs; however, only 7 of these studies had mental function as an outcome. Six studies that investigated non-psychiatric outcomes or mental health without nutritional intervention were excluded from the analysis.

A comprehensive analysis of seven studies revealed that the predominant themes were depression and obesity, with probiotics identified as the most prevalent intervention. The observation period ranged from 8 weeks to 12 weeks, with the majority of the studies focusing on short-term effects. A comprehensive list of the RCTs that were incorporated into the review is provided in Table 1[8-14]. A synthesis of the results revealed that probiotics exhibited a modest effect on cognition, while prebiotics demonstrated minimal impact. The following section presents an overview of the included studies.

Table 1 List of articles included in the analysis

Ref.	Sample size	Study design	Outcome assessment	Conclusions
Rudzki *et al* [8], 2019	Patients with depression were randomized to receive either the probiotic *Lactobacillus Plantarum* 299v plus an SSRI (n = 30) or placebo plus an SSRI (n = 30) for 8 weeks	Psychiatric symptoms were assessed using the Hamilton Depression Rating Scale, Symptom Checklist and Perceived Stress Scale. Cognitive function was assessed using the Attention and Perceptivity Test, Stroop Test. Biochemical markers measured included tryptophan, kynurenine	There was a significant decrease in kynurenine concentration in the *Lactobacillus Plantarum* 299v group compared to the placebo group. Results of post hoc analysis did not reach statistical significance in neither probiotic nor placebo group. There were no significant changes of TNF-α, IL-6, and IL-1β and cortisol concentrations in neither probiotic nor placebo groups	Augmentation of SSRI treatment with probiotic bacteria *Lactobacillus Plantarum* 299v improved cognitive performance and decreased kynurenine concentration
Lee *et al* [14], 2022	The study involved 17 subjects with major depressive disorder (aged 60 years or older, 41.2% female) and received levomirasipran or placebo for 12 weeks	To determine if changes in gut microbiota occur with remission in geriatric depression	Baseline enrichment of *Faecalibacterium*, *Agathobacter*, and *Roseburia* relative to a reference frame was associated with treatment outcome of remission	Fecal microbiota as a potential predictor of treatment response in geriatric depression
Vaghef-Mehrabani *et al*[13], 2023	45 women with obesity and major depression	Patients were assigned to consume either inulin or maltodextrin at a dose of 10 g per day for 8 weeks. All patients also consumed a healthy calorie-restricted diet. Anthropometric measurements, food intake, depression, lipopolysaccharide, inflammatory biomarkers (TNF-α, IL-10, monocyte chemoattractant protein-1, Toll-like receptor-4, high-sensitivity C-reactive protein), and BDNF were measured	Weight loss and Hamilton Depression Rating Scale scores decreased in both groups, with non-significant between-group differences at the end of the study	In a short-term study, prebiotic supplementation had no significant beneficial effects on depressive symptoms, intestinal permeability, or inflammatory biomarkers in obese and depressed women
Badrfam *et al*[11], 2024	60 hospitalized patients with a history of methamphetamine use for 3 years or more	Brief Psychiatric Rating Scale, Beck Anxiety Inventory, Pittsburgh Sleep Quality Index were evaluated under treatment with Probiotic *Lactobacillus acidophilus* with risperidone	Patients who took probiotics had better quality sleep, increased appetite, and a higher BMI, but there were no statistically significant differences between the two groups when it came to improvement in psychiatric and anxiety symptoms	The use of probiotics was associated with improved sleep quality, increased appetite, and increased BMI in patients with chronic methamphetamine use
Sevillano-Jiménez *et al*[39], 2022	A randomized clinical trial of a group of 50 people diagnosed with schizophrenia spectrum disorder during the severe acute respiratory syndrome-coronavirus 2 restriction period	Assessment of cardiovascular event risk factors in a personalized nutrition education program rich in prebiotics and probiotics (*e.g.*, dairy products, fermented foods, green leafy vegetables, high-fiber fruits, and whole grains)	A 27.4% reduction in the prevalence of metabolic syndrome risk factors in all its components was evidenced, leading to a clinically significant improvement (decrease in cardiovascular risk) in the intervention group at 6 months	The development of a nutritional program focused on increasing the dietary content of prebiotics and probiotics effectively improves the cardio-metabolic profile in schizophrenia spectrum disorders
Hwang *et al* [10], 2019	A 12-week intervention for 100 patients with mild cognitive impairment	*Lactobacillus plantarum* C29 fermented soy (DW2009) was administered as a dietary supplement for cognitive enhancement, and the composite score of cognitive function related to memory and attention measured by computerized neurocognitive testing and BDNF levels were measured	DW2009 group showed greater improvements in the combined cognitive functions, especially in the attention domain. Cognitive improvement was associated with increased serum BDNF levels	DW2009 can be safely administered to enhance cognitive function in individuals with MCI. Increased serum BDNF levels after administering DW2009 may provide preliminary insight into the underlying effects of cognitive improvement, which suggests the importance of the gut-brain axis in ameliorating cognitive deficits in MCI
Freijy *et al* [12], 2024	An 8-week trial of probiotics and prebiotics in 118 depressed adults	At baseline and 8 weeks, the Cogstate Brief Battery was administered, testing processing speed, attention, visual learning, and working memory. Data were analyzed using Bayesian linear regression	Weak evidence that the probiotic improved working memory. For the other treatments, there was little or no evidence of cognitive improvement. Weak evidence that the prebiotic diet impaired processing speed	A probiotic-induced improvement in working memory, and prebiotic-induced impairment in processing speed. However, the evidence remains inconclusive regarding any cognitive benefit or harm induced by the probiotic, prebiotic diet, or synbiotic treatments

BDNF: Brain-derived neurotrophic factor; BMI: Body mass index; IL: Interleukin; MCI: Mild cognitive impairment; SSRI: Selective serotonin reuptake inhibitor; TNF-α: Tumor necrosis factor alpha.

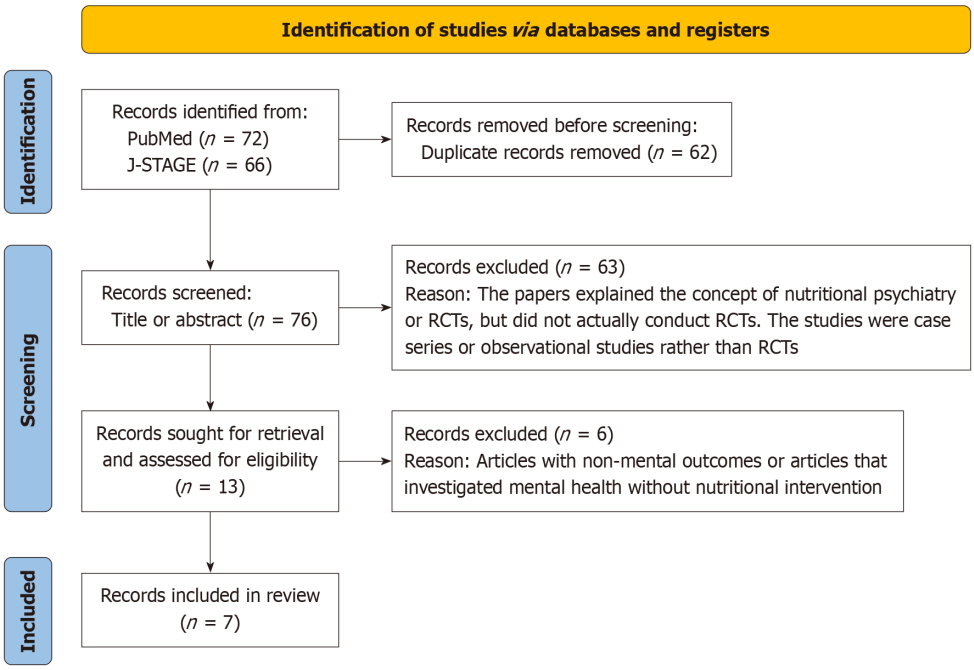


Figure 1 Flow diagram for the review, which included searches of databases and registers. RCTs: Randomized controlled trials.

In an RCT that examined the effects of combining probiotics (LP299v) with selective serotonin reuptake inhibitors for depression, no enhancement of the antidepressant effect was observed. However, cognitive function measured by the Stroop Test and other methods improved compared to placebo[8]. The RCT comprised 30 patients in each of the probiotic and placebo groups, with a treatment period spanning 8 weeks. Tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and IL-1β, which were measured as inflammatory markers, remained unchanged. However, a significant reduction in blood kynurenine concentrations was observed in the probiotic group, which correlated with improved cognitive function. Kynurenine, a substance produced during the metabolism of the essential amino acid tryptophan in the body, is a notable component of this pathway. Tryptophan is also a raw material for the neurotransmitter serotonin, and its metabolism is related to mental function and plays an important role in mood and sleep. In patients diagnosed with depression, the pathway that metabolizes tryptophan to kynurenine is overactivated[15]. This overactivation has been linked to the conversion of kynurenine into neurotoxic substances that can damage nerve cells. The potential for probiotics to enhance tryptophan metabolism and reduce kynurenine levels in the intestinal environment is a promising avenue for further research. However, this effect did not result in an increase in clinical antidepressant effects.

In an RCT that involved 100 individuals with mild cognitive impairment (MCI), cognitive function was evaluated over a 12-week period using computerized neurocognitive function tests. The participants were administered either a plant-derived probiotic, *Lactobacillus plantarum* C29 fermented soy (DW2009), or a placebo. The results showed that the attention domain of cognitive function exhibited significant improvement[10]. Serum brain-derived neurotrophic factor (BDNF) levels were found to be associated with the observed enhancement in cognitive function. The potential for probiotics derived from fermented foods to enhance cognitive functions in MCI patients is a promising avenue for further research.

In an RCT involving 60 inpatients with a history of more than 3 years of methamphetamine use, probiotic capsules or placebo were administered for a period of 8 weeks in conjunction with risperidone. The psychiatric symptoms, sleep, and appetite of the participants were measured using the Brief Psychiatric Rating Scale (BPRS). The Beck Anxiety Inventory (BAI), Pittsburgh Sleep Quality Index, and Simple Appetite Nutritional Questionnaire were used to assess psychiatric symptoms, sleep quality, and appetite, respectively. The results indicated that the probiotic group exhibited enhancements in sleep quality, heightened appetite, and an augmented body mass index[11]. However, no alterations were observed in the BPRS or BAI. The study's findings indicate that probiotics did not improve psychiatric or anxiety symptoms in methamphetamine users, yet they did enhance sleep quality and physical well-being.

In an RCT that examined the effects of prebiotics and probiotics on cognitive function, probiotics were found to improve cognitive function[12]. This RCT involved 118 adults with low mood, and four groups were compared, each receiving a combination of two of the following three interventions: (1) A probiotic supplement; (2) A high-prebiotic diet; and (3) Placebo. The treatment period spanned 8 weeks, and cognitive function was measured using the Cogstate Brief Battery. The probiotic supplement demonstrated a significant enhancement in working memory. Conversely, the high-prebiotic diet exhibited a detrimental effect on processing speed. The synbiotic group, which received a combination of a probiotic supplement and a high-prebiotic diet, exhibited no alterations in cognitive function. In adults experiencing low mood, probiotics exhibited a mild effect, while synbiotics in combination with a high-prebiotic diet demonstrated no significant impact. Consequently, these findings indicate that, in contrast to probiotics, the administration of prebiotics exerts minimal influence on enhancing cognitive function. In a similar vein, the administration of prebiotics in isolation has demonstrated minimal antidepressant efficacy. In an RCT investigating the efficacy of prebiotics in treating

depression associated with obesity, the effect was comparable to that of a placebo[13]. In this study, 45 obese women with major depression were randomly assigned to receive either 10 g of the prebiotic inulin or 10 g of placebo maltodextrin per day for 8 weeks. All patients adhered to a nutritionally balanced diet that was calorie-restricted, and serum levels of zonulin, lipopolysaccharide, inflammatory biomarkers (TNF-α, IL-10, monocyte chemoattractant protein-1, Toll-like receptor-4, and high-sensitivity C-reactive protein), and BDNF were measured before and after the intervention. The results indicated that both prebiotics and placebo led to a mild reduction in weight and antidepressant effects. However, these effects were comparable between the two groups, and no significant differences were observed in inflammatory marker levels. It is noteworthy that prebiotics do not exert a direct influence on the gut microbiota, in contrast to the action of probiotics, which may diminish their efficacy.

In an RCT that compared the response of 17 depressed patients aged 60 years or older to levomilacipran or placebo over a 12-week period, the fecal microbiota of the group in remission from depression exhibited higher levels of *Faecalibacterium*, *Agathobacter*, and *Roseburia* prior to the intervention[14]. Differential abundance analysis revealed significant changes at the genus level from baseline to post-treatment in patients in remission from depression, but no changes were observed in non-remission patients. The alterations in the composition of the gut microbiota appear to be closely associated with the response to antidepressant treatment. The emergence of an antidepressant effect is contingent on the presence of specific bacterial taxa within the gut microbiota prior to intervention, along with a subsequent shift in the composition of the gut microbiota following intervention.

DISCUSSION

Current status of RCTs in nutritional psychiatry

Nutrition, akin to lifestyle habits, is a modifiable factor that can be addressed through intervention. Nutritional psychiatry, a relatively recent field of study, utilizes dietary modifications and supplements to address mental health concerns. Deficiencies in specific nutritional elements have been demonstrated to impair cognitive function and have been linked to the emergence of various mental health conditions. For instance, deficiencies in vitamin D and omega-3 fatty acids have been linked to an increased risk of depression, while vitamin B_{12} deficiency has been associated with impaired memory and reduced cognitive ability. Magnesium deficiency has been linked to increased anxiety and irritability[16]. However, the evidence on the aforementioned nutritional factors and mental function is predominantly derived from observational studies, which hinders the ability to eliminate confounding factors and elucidate the causal relationship.

RCTs have been demonstrated to minimize the influence of confounding factors and demonstrate a causal relationship. Consequently, a scoping review of RCTs in the domain of nutritional psychiatry research was conducted. The findings revealed a paucity of evidence from RCTs concerning the relationship between nutrients and mental function. The majority of RCTs were grounded in interventions targeting the gut microbiota, employing probiotics and prebiotics. Probiotic interventions have been demonstrated to enhance specific domains of cognitive function, including working memory and attention. However, these interventions have not yielded improvements in psychiatric symptoms. As biomarkers, interventions with nutritional factors such as probiotics have been shown to alter the gut microbiota. In individuals with depression, there has been a decrease in kynurenine and an increase in BDNF, but no improvement has been confirmed in intestinal permeability or various inflammatory markers that affect psychiatric symptoms. The biological pathways through which nutritional factors may induce psychiatric symptoms include inflammation, oxidative stress, epigenetic changes, and neuroplasticity, often mediated through the microbiota-gut-brain axis[17-19]. However, the efficacy of short-term nutritional interventions in modulating these biological pathways remains to be elucidated.

RCTs in the field of nutritional psychiatry are characterized by the presence of numerous potential factors, confounding exposures, and relatively modest individual effect sizes. Consequently, these RCTs are unable to reach the same conclusions as RCTs in conventional pharmacological studies. Nevertheless, the inability to preclude false negative outcomes due to inadequate statistical power and false positive results attributable to biased designs persists in RCTs of nutritional psychiatry.

Mendelian randomization trials as a complement to RCTs

In instances where it is challenging to draw conclusions from RCTs, the advent of genetic research has led to the utilization of Mendelian randomization (MR) trials as a means to estimate causal relationships[20]. RCTs and MR studies represent two research designs that provide randomized evidence in the realm of human biological and medical research. MR utilizes genetic markers that are reliably associated with specific, potentially modifiable exposures as instrumental variables to assess the relationship between exposure and outcome. A key advantage of MR is its ability to reduce bias, as alleles are randomly assigned at conception, thereby ensuring the independence of the outcome variable from confounding factors.

MR studies are currently being conducted to ascertain whether nutritional factors, including vitamin D, folate, serum magnesium, copper, triglycerides, and glucose metabolic pathways, are associated with the emergence of psychiatric symptoms. For instance, Alzheimer's disease and vitamin D, schizophrenia and vitamin B_6, and mood disorders and trace elements have been examined using MR trials[21-23]. However, the causal relationship between these nutritional factors and the development of psychiatric symptoms remains unclear. A primary reason for this is that many nutritional factors do not demonstrate a linear relationship between exposure and outcome. Consequently, the inferential process of determining causation through conventional MR analysis necessitates a linear relationship between exposure and outcome. However, the relationship between cognitive function and vitamin D is not linear, as both deficiency and excess

have been demonstrated to be deleterious[24].

Although MR is not a substitute for RCTs in detecting causal relationships, it can be a useful method to estimate whether dietary factors are causally related to psychiatric symptoms in nutritional psychiatry, where it is difficult to design effective RCTs due to potential confounding factors[25]. Consequently, the development of novel MR research methodologies that address nonlinearity, such as the fractional polynomial method and the piecewise linear method, is of paramount importance in the nutritional psychiatry research.

Exploring mechanisms in fundamental research

To enhance the precision of RCTs, it is imperative to elucidate the mechanism of action of nutritional factors through fundamental research. The elucidation of the mechanism of action of nutritional factors through fundamental research is instrumental in the development of an effective RCT design.

This review of RCTs also indicates that probiotics may be effective in improving cognitive function, but no significant impact on psychiatric symptoms. However, case reports have demonstrated that probiotics can significantly improve the psychiatric symptoms associated with schizophrenia in some patients. A case study that administered a probiotic containing three different bacterial strains to patients with schizophrenia and gut dysbiosis (gastrointestinal symptoms), intestinal barrier dysfunction (history of bacterial translocation), and central dopamine nervous system dysfunction (*e.g.*, cognitive dysfunction) found that the probiotic improved psychiatric symptoms in parallel with changes in gut microbiota patterns[26]. Given our knowledge of the specific bacterial strain, we can investigate the underlying mechanism by which probiotic colonization of germ-free mice leads to the alleviation of psychiatric symptoms. The probiotic strains utilized in this study were *Bacillus subtilis* TO-A, *Enterococcus faecium* T-110, and *Clostridium butyricum* TO-A[27]. The colonization of germ-free mice with these bacteria resulted in an augmentation of neural stem cells, in comparison to the number observed in specific pathogen-free mice raised under standard conditions[28]. The augmentation in neural stem cells serves as a model for adult neurogenesis, a process implicated in memory and emotional regulation[29]. In a metabolomics analysis, 16 metabolites, including theanine, carnosine, and 3-hydroxybutyric acid, were identified in the blood of mice colonized with the three types of probiotics compared to germ-free mice. Subsequent administration of theanine, carnosine, and 3-hydroxybutyric acid to human-derived neural stem cells resulted in the promotion of neural stem cell differentiation into neurons. These findings from basic research suggest that the three types of probiotics induce adult neurogenesis through their metabolites[28]. While probiotics do not directly enhance brain function, they do so by facilitating neurogenesis through various mediators. If the mediators are predicted through fundamental research, then when assembling an RCT with the probiotics, a more accurate RCT can be designed by adding measurements of the mediators. The findings of fundamental research provide indispensable information for the effective design of RCTs (Figure 2).

Therefore, gut microbiota plays a crucial role in mental health. The gut-brain axis, a complex communication network between the gut and brain, highlights this connection. An imbalance in gut microbiota, known as dysbiosis, has been linked to mental health issues like anxiety, depression, and even neurodevelopmental conditions. Gut microbiota produces neurotransmitters, chemical messengers that regulate mood, emotions, and cognition. Gut microbiota ferments fiber, producing short-chain fatty acids (SCFAs) that have anti-inflammatory and gut-protective properties. SCFAs can also influence brain function and mood. Moreover, gut microbiota influences the immune system, reducing inflammation and oxidative stress that can negatively impact brain function. To summarize the above and show a conceptual diagram of the current state of nutritional psychiatry, RCTs on healthy diets, probiotics, prebiotics, and nutrient interventions are still insufficient to build evidence, and it is important to plan effective RCTs using the results of Mendelian randomized trials and basic research.

Effective RCTs of nutritional psychiatry are scarce, but the need for them is growing. In the 21st century, there has been a marked increase in public interest in mental health[30]. Mental illness exerts a substantial influence on individuals' lives, concurrently imposing a considerable socioeconomic burden[31]. The low response rate and adverse effects associated with drug therapy in the field of psychopharmacology have impeded the reduction of this socioeconomic burden. This underscores the imperative for novel intervention methods that do not rely on drug therapy for addressing mental illness. In 2015, the World Psychiatry organization advanced the theory of nutritional psychiatry, which posits the notion of leveraging nutritional interventions to prevent and treat mental illness[32]. This theory underscores the necessity to develop customized nutritional intervention programs tailored to individual patients. While the factors that determine mental health are complex, there is a strong association between an unhealthy diet and the worsening of mood disorders, such as anxiety and depression, and other neuropsychiatric disorders. However, the study noted that, despite the 2015 recommendation by World Psychiatry organization, there is a paucity of effective RCTs in nutritional psychiatry with sufficient detection power. There is an absence of compelling evidence to support the notion that interventions tailored to specific nutritional factors exert a favorable influence on mental health. The heterogeneity of study results and variation in the quality of evidence pose challenges for study planning and clinical decision-making. Consequently, a comprehensive and systematic understanding of nutrition and psychiatric disorders remains elusive.

The necessity for high-quality, adequately powered RCTs is evident to establish a robust evidence base for nutritional psychiatry. Observational and basic research have demonstrated that inflammation, oxidative stress, gut microbiota, mitochondrial dysfunction, and neuroplasticity are potential mechanisms by which nutritional factors affect psychiatry [33-35]. The design of RCTs should be informed by these hypothesized mechanisms to ensure the relevance and validity of the research findings. The design of RCTs using such markers is crucial for substantiating the efficacy of nutritional interventions in psychiatry. The utilization of evidence derived from valid RCTs has the potential to contribute to the prevention and treatment of psychiatric disorders, thereby reducing the socioeconomic burden associated with these conditions.

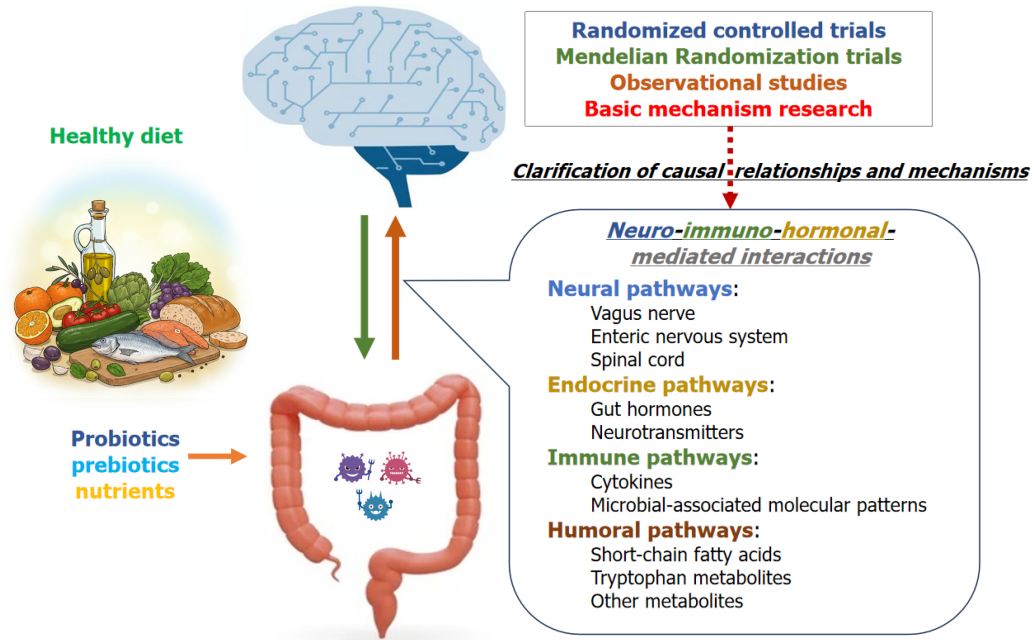


Figure 2 Schematic diagram of mechanisms and research methods in nutritional psychiatry.

Current dietary strategies and origins of the idea of nutritional psychiatry

Dietary strategies can be a valuable tool in the treatment of mental illness. People with mental illness should be screened for nutritional deficiencies. This can be done using a variety of methods, such as a dietary questionnaire or a blood test. A detailed dietary history should be obtained from all patients. This should include information about the patient's usual food intake, as well as any food allergies or intolerances. An assessment of gut health may also be helpful. This can be done using a variety of methods, such as a stool test or a breath test. Thus, individuals with mental illness should be provided with individualized dietary counseling. This should include education about the importance of a healthy diet for mental health, as well as specific recommendations for dietary changes. In some cases, nutritional supplementation may be necessary to correct nutritional deficiencies. Probiotics may be helpful for improving gut health and cognitive function. Individuals with mental illness could be encouraged to make dietary changes that are sustainable and easy to adhere to, such as eating a variety of fruits, vegetables, and whole grains[36]. Outcome measures, such as mood scales and cognitive tests, can be used to assess the effectiveness of the dietary intervention. Specific dietary recommendations for mental illness include below. For depression, a diet rich in omega-3 fatty acids, B vitamins, and vitamin D may be helpful for improving mood and reducing symptoms of depression. For anxiety, a diet that is low in processed foods and high in fruits, vegetables, and whole grains may be helpful for reducing anxiety symptoms. For bipolar disorder, a diet that is low in processed foods and high in fruits, vegetables, and whole grains may be helpful for stabilizing mood. For schizophrenia, a diet that is low in processed foods and high in fruits, vegetables, and whole grains may be helpful for improving cognitive function and reducing symptoms of schizophrenia. For attention-deficit hyperactivity disorder, a diet that is low in processed foods and high in fruits, vegetables, and whole grains may be helpful for improving attention and reducing hyperactivity. For autism spectrum disorder, a gluten-free and casein-free diet may be helpful for some children with autism spectrum disorder[37].

The idea of nutritional psychiatry owes its origins to the work of two great men named Rudolf. The human body is incapable of sustaining its functions without a constant infusion of nutritional elements. As posited by the German theoretical physicist Rudolf Clausius, the natural world is governed by the law of increasing entropy. To maintain function, energy must be continuously infused to reduce entropy[38]. In adults, the infused energy is replaced by elements that comprise the body's proteins, in addition to energy, as demonstrated by the experiments of Rudolph Schoenheimer. Schoenheimer's experiments demonstrated that when adult mice were fed food containing nitrogen-15-labeled leucine, only 29.6% of the nitrogen-15 administered was excreted in urine and feces, while more than half, 56.5%, was incorporated into the proteins that make up the body[39]. It is noteworthy that approximately half of the proteins comprising a mouse's entire body are replaced with new proteins over a period of 3 days. The necessity for organisms to undergo constant change at the elemental level through nutrition to ensure survival and functionality is underscored by this observation. This underscores the significance of nutrients at a molecular level in preserving bodily functions. Evidence-based nutritional factor interventions should be considered as cost-effective mental health measure. However, as demonstrated in this scoping review, there is currently a paucity of established evidence in the field of nutritional psychiatry. Consequently, there is a pressing need to devise and validate novel RCT protocols through the refinement of measurement factors, informed by the findings of MR research, fundamental research, and epidemiological research.

Limitations of the study

This study had several limitations. First, the fact that no rigorous RCTs on diet were found in nutritional psychiatry

research is a major limitation of this review. Second, this scoping review employed the search term "nutritional psychiatry," which resulted in the exclusion of articles that did not include this term. A concept analogous to nutritional psychiatry is psychobiotics, and it is imperative to augment the number of analogous search terms and conduct further investigations. Finally, no search was conducted for ongoing clinical trials. Although the search did result in registered RCTs and protocol-level articles, these were not included in this review as the results are not yet available.

CONCLUSION

A review of RCTs in nutritional psychiatry has demonstrated that probiotics have been shown to modify gut microbiota patterns and enhance cognitive function *via* the microbiota-gut-brain axis. There has been minimal improvement in the psychiatric symptoms observed; however, the quality and quantity of RCTs in nutritional psychiatry are inadequate. The challenge in conducting effective RCTs in this field is believed to stem from the presence of numerous confounding factors, including lifestyle influences, and the relatively modest effect sizes of specific nutritional factors on mental status. To bolster the evidence in nutritional psychiatry, it would be advantageous to disseminate the findings of nonlinear MR studies and fundamental research into the development of effective RCTs.

FOOTNOTES

Author contributions: Nagamine T designed and conceived the study, collected the data, analyzed and interpreted the results, drafted the manuscript, and has read and agreed to the published version of the manuscript.

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SYSTEMATIC REVIEWS

Safety and efficacy of glucagon-like peptide-1 receptor agonists in individuals with type 2 diabetes mellitus fasting during Ramadan: a systematic review and meta-analysis

Abul Bashar Mohammad Kamrul-Hasan, Joseph M Pappachan, Hamid Ashraf, Lakshmi Nagendra, Deep Dutta, Mohammad Shafi Kuchay, Shehla Shaikh

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Abstract

BACKGROUND

Data on the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in individuals with type 2 diabetes mellitus (T2DM) during Ramadan fasting is limited. No meta-analysis has summarized the safety and effectiveness of GLP-1RAs in these situations.

AIM

To evaluate the safety and efficacy of GLP-1RA in patients with T2DM fasting

during Ramadan.

METHODS
Electronic databases were systematically searched for relevant studies that featured GLP-1RA in the intervention arm and other glucose-lowering medications in the control arm. The primary outcome was adverse events (AEs) during Ramadan for both groups; other outcomes included changes in glycemic and anthropometric measures during the peri-Ramadan period.

RESULTS
Four studies [three randomized-controlled trials with low risk of bias (RoB) and one prospective observational study with serious RoB] involving 754 subjects were analyzed. GLP-1RA group achieved greater glycated hemoglobin reduction than the non-GLP-1RA group [mean difference (MD): -0.31%, 95%CI: -0.61 to -0.01, $P = 0.04$, $I^2 = 77\%$] with a lower risk of documented symptomatic hypoglycemia (risk ratio = 0.38, 95%CI: 0.16 to 0.88, $P = 0.02$). Any AEs, serious AEs, or AEs that led to treatment discontinuation were comparable between the two groups. The GLP-1RA group experienced greater weight loss compared to the non-GLP-1RA group (MD: -2.0 kg, 95%CI: -3.37 to -0.63, $P = 0.004$, $I^2 = 95\%$). There were comparable changes in blood pressure and lipid profile between the two groups. GLP-1RA users experienced higher risks of gastrointestinal AEs, nausea, and vomiting; however, the risks of heartburn, abdominal pain, and diarrhea were similar in both groups.

CONCLUSION
Limited evidence suggests that GLP-1RAs are safe for T2DM management during Ramadan, offering modest benefits in blood sugar control and weight loss. Large multicenter trials are needed to confirm their safety and efficacy in at-risk populations, improving clinical practice decision-making.

Key Words: Type 2 diabetes mellitus; Glucagon-like peptide-1 receptor agonist; Ramadan; Religious fasting; Safety; Meta-analysis

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Core Tip: No systematic review and meta-analysis (SR/MA) have previously assessed the safety and efficacy of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in individuals with type 2 diabetes mellitus who fast during Ramadan. This SR/MA of 4 studies with 754 participants identified that GLP-1RAs are safe with only exaggerated gastrointestinal side effects, mainly nausea and vomiting. GLP-1RA also appears to be effective in improving glycated hemoglobin and aiding in weight loss, compared to other glucose-lowering medications. However, other cardiometabolic benefits, such as improvements in blood pressure and lipid profile, were not evident. Larger multinational, randomized trials with broader global participation are needed to establish more definitive clinical practice recommendations for using GLP-1RAs during Ramadan fasting.

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INTRODUCTION

Fasting during Ramadan (the ninth month in the Islamic lunar calendar) is one of the five pillars of the Islamic religious faith. During Ramadan, all adult Muslims are required to abstain from consuming food and drink (including medication) from sunrise to sunset[1]. It is estimated that there are approximately 148 million Muslims who live with diabetes worldwide. The fasting duration varies by geographic location and can last up to 19 hours a day in some parts of the world, especially during the summer. The lifestyle changes in Ramadan, especially abstinence from food and drink for long fasting hours and using glucose-lowering drugs (GLDs) for diabetes treatment, may predispose these individuals to develop adverse events (AEs), including dehydration and hypoglycemia[2]. The Diabetes and Ramadan (DaR) 2020 survey, which involved 5865 participants, found that 83.6% of those surveyed fasted during Ramadan, 94.8% fasted for 15 days or more, and 61.9% completed the entire month[3]. Many of these individuals are at risk of developing complications related to fasting and often fast despite medical advice not to do so[4,5]. Consequently, this sizable Muslim population with diabetes that observes fasting during Ramadan needs special attention before and throughout Ramadan.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are highly recommended for patients with type 2 diabetes mellitus (T2DM) by all guidelines, given their glycemic, weight, cardiorenal, hepatic, and metabolic benefits[6]. The use of

GLP-1RAs continues to increase[7], and it is presumed that many Muslims with T2DM fasting during Ramadan will utilize these medications. The reduced risk of hypoglycemia and the additional benefit of weight loss or weight maintenance confer an extra advantage when continuing their use during Ramadan[6]. According to guidelines from the International Diabetes Federation and the DaR International Alliance, the use of GLP-1RAs confers no additional risk for fasting, a view that has also been reiterated in the American Diabetes Association's recommendations for fasting[6,8]. The guidelines also recommend against initiating GLP-1RAs just before Ramadan, given their tolerability issues, especially gastrointestinal (GI) ones, which may make fasting troublesome for the patient and potentially negate the fast[8].

However, data on GLP-1RA use by patients with T2DM during Ramadan fasting is limited. Due to the limited number of randomized controlled trials (RCTs) and observational studies with small sample sizes specifically addressing the adverse effects and efficacy of GLP-1RAs in individuals with T2DM who fast during Ramadan, we conducted this systematic review and meta-analysis (SR/MA). Our goal was to investigate whether individuals with T2DM using GLP-1RAs during the fasting month of Ramadan achieve glycemic and other metabolic benefits, with or without an increased risk of adverse effects/events.

MATERIALS AND METHODS

Study setting

This SR/MA was conducted following the procedures described in the Cochrane Handbook for Systematic Reviews of Interventions and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[9,10]. The SR/MA has been registered with PROSPERO (CRD42024637706), and the protocol summary can be accessed online.

Ethical compliance

No separate ethical approval was needed for this MA, as such approvals already exist for the individual included studies.

Search strategy

A systematic search was conducted across various databases and registers, including MEDLINE (*via* PubMed), Embase, Web of Science, and ClinicalTrials.gov. This search spanned from the inception of each database to December 25, 2024. Using the Boolean operators "AND" and "OR" the following terms were searched: (1) "Glucagon-like peptide-1 receptor agonists"; (2) "GLP-1 receptor agonists"; (3) "GLP-1RA"; (4) "Exenatide"; (5) "Lixisenatide"; (6) "Liraglutide"; (7) "Albiglutide"; (8) "Dulaglutide"; (9) "Semaglutide"; (10) "Tirzepatide"; (11) "Ramadan fasting"; (12) "Religious fasting"; (13) "Type 2 diabetes mellitus"; (14) "Type 2 diabetes"; (15) "Type II diabetes"; (16) "T2DM"; and (17) "T2D". The search terms were applied to titles and abstracts. The aim was to identify published and unpublished studies in English. Additionally, the search involved reviewing references within the published articles retrieved for this study and relevant journals.

Study selection

The Population, Intervention, Comparison, Outcomes, and Study design was used as a framework to formulate eligibility criteria for studies in this SR/MA. The patient population (P) consisted of adults of either sex with T2DM fasting during Ramadan; the intervention (I) was any GLP-1RA either as monotherapy or combined with other GLDs for managing T2DM; the comparison or control (C) group comprised individuals receiving GLDs other than a GLP-1RA either as monotherapy or in combination; the outcomes (O) included safety and/or effectiveness of study drugs during the study period; and RCTs or prospective observational/intervention studies were considered as the study type (S) for inclusion. The studies must have at least two arms: (1) One with any GLP-1RA alone or combined with other GLDs (GLP-1RA group); and (2) The other(s) with other GLDs either as monotherapy or combination therapy (non-GLP-1RA group). Exclusion criteria were case reports or case series, retrospective studies, studies conducted in type 1 or other types of diabetes, including patients with both type 1 and type 2 diabetes, studies conducted among pregnant or lactating women, studies without a non-GLP-1RA control arm, and studies not reporting the outcomes of interest. Four review authors independently identified eligible articles according to the above criteria. Discrepancies in opinion on the inclusion of studies were resolved by consensus.

Data extraction

Four review authors conducted data extraction independently by using standardized data extraction forms. The results were consolidated upon identifying multiple publications from a single study group, and relevant data from each article were incorporated into the analyses. The following data were extracted for all the eligible studies and included in the review: (1) First author; (2) Year of publication; (3) The country where the study was conducted; (4) Study design; (5) Major inclusion criteria of the study subjects; (6) GLDs used in the GLP-1RA and non-GLP-1RA groups; (7) sample size; (8) Number of male and female participants; (9) Mean age; (10) Diabetes duration; (11) Body weight; (12) Glycated hemoglobin (HbA1c); (13) Systolic and diastolic blood pressure (BP); (14) Lipid profile; and (15) AEs, including hypoglycemia. Any disagreements were resolved by consensus.

Dealing with missing data

The necessary supplementary files of the articles were obtained from the websites of the publishing journals. Further

information, if needed, was collected from the corresponding authors of the relevant articles *via* email. All pertinent information collected in this manner was meticulously incorporated into the MA. Moreover, attrition rates, encompassing dropouts, losses to follow-up, and withdrawals, were meticulously examined.

Outcomes analyzed

The primary outcome of interest was the risk of any AEs, including hypoglycemia, in the GLP-1RA group compared to the non-GLP-1RA group. Additional outcomes included the mean difference (MD) of changes in glycated hemoglobin (HbA1c), body weight, systolic and diastolic BP, and lipid profile from baseline between the two groups.

Statistical analysis

The results of the outcomes were reported using risk ratios (RRs) for dichotomous variables and MDs for continuous variables, together with 95% confidence intervals (CIs). The Review Manager computer program, version 7.2.0, was used to generate forest plots, which portrayed the RR or MD for the outcomes; the left side of the forest plot favored the GLP-1RA group, and the right side favored the non-GLP-1RA group[11]. Random-effects analysis models were chosen to address the anticipated heterogeneity resulting from variations in population characteristics and study lengths. The inverse variance statistical method was applied for all instances. The SR/MA encompassed forest plots that integrated data from at least two trials. A significance level of $P < 0.05$ was used.

Assessment of the risk of bias in the included studies

Three authors independently conducted the risk of bias (RoB) assessment using the Cochrane RoB tool for randomized trials, Version 2 (RoB2), and the RoB in Non-randomized Studies of Interventions, Version 2 (ROBINS-I V2), for the RCTs and non-randomized intervention trials, respectively[12,13]. In discrepancies, the sixth and seventh authors acted as arbitrators to achieve consensus. The RoB VISualization (robvis) web app created RoB plots[14].

Assessment of heterogeneity

The assessment of heterogeneity was initially conducted by studying forest plots. Subsequently, a χ^2 test was performed using N-1 degrees of freedom and a significance level of 0.05 to determine the statistical significance. The I^2 test was also employed in the subsequent analysis[15]. The specifics of understanding I^2 values have been explained in depth elsewhere[16].

RESULTS

Search results

The PRISMA flow diagram of steps in selecting the studies are depicted in Figure 1. The initial search identified 103 articles, narrowed to six after screening titles, abstracts, and subsequent full-text reviews. Finally, four studies involving 754 subjects meeting all the prespecified criteria were included in this SR/MA[17-20]. Two studies were excluded- one did not have a non-GLP-1RA comparator group, and the other was a substudy of an included study[21,22].

Characteristics of included and excluded studies

The specifics of the included and excluded studies are shown in Table 1[17-20] and Supplementary Table 1[21,22], respectively. Three included studies were randomized, parallel-group, open-label, active-controlled trials[17,18,20]; the other was an open-label, single-center, two-arm parallel-group, prospective observational study[19]. All studies had two arms: (1) One with any GLP-1RA alone or combined with other GLDs (GLP-1RA group); and (2) The other with GLDs other than GLP-1RA either as monotherapy or combination therapy (non-GLP-1RA group). In the GLP-1RA arm, two studies used liraglutide[17,20], one used lixisenatide[18], and the other used semaglutide[19]. The follow-up duration of the studies ranged from 12-33 weeks.

RoB of the included studies

Supplementary Figure 1 depicts the RoB across the four studies included in the MA. The overall RoB, assessed by the RoB2 tool, was low in all three RCTs in this SR/MA. The non-randomized prospective trial included in this SR/MA had a serious overall RoB stemming from bias due to confounding, as evaluated by the ROBINS-I assessment tool. Publication bias evaluation was not conducted due to insufficient RCTs (fewer than 10) in the forest plots[23].

Safety of GLP-1RA

The comparison of the proportions of study subjects in the GLP-1RA and non-GLP-1RA groups experiencing AEs during Ramadan fasting is summarized in Table 2. Identical proportions of study subjects in the GLP-1RA and non-GLP-1RA groups had any AEs, serious AEs, or AEs leading to treatment discontinuation. Study subjects in the GLP-1RA group had higher risks of GI AEs [RR = 5.27, 95%CI: 1.40 to 19.89, I^2 = 50% (low heterogeneity), P = 0.01], nausea [RR = 14.05, 95%CI: 2.69 to 73.33, I^2 = 0% (not important heterogeneity), P = 0.002], and vomiting [RR = 5.96, 95%CI: 1.05 to 33.77, I^2 = 0% (not important heterogeneity), P = 0.04] than those in the non-GLP-1RA group. However, the risks of heartburn, abdominal pain, and diarrhea were not statistically increased in the GLP-1RA group compared to the non-GLP-1RA group. Compared to the non-GLP-1RA group, the GLP-1RA group had a lower risk of documented symptomatic hypoglycemia [RR = 0.38, 95%CI: 0.16-0.88, I^2 = 45% (low heterogeneity), P = 0.02]; however, the risk of any hypoglycemia was statist-

Table 1 Baseline characteristics of individual studies and study participants included in the meta-analysis

Ref.	Study design, trial reg. number (if any)	Major inclusion criteria	Groups	GLD used	*n*	Sex	Age (years), mean (SD)	Duration of diabetes mellitus (years), mean (SD)	Baseline body weight (kg), mean (SD)	Baseline HbA1c (%), mean (SD)	Study duration
Azar *et al*[17], 2016, LIRA-Ramadan, 39 sites in 7 countries	Randomized, parallel-group, open-label, active-controlled trial, NCT01917656	Age 18-80 years, HbA1c 7%-10%, body mass index ≥ 20 kg/m^2, on stable diabetes treatment (MFN ≥ 1 gm + SU MTD)	GLP-1RA	Liraglutide 18 mg + MFN	171	M: 85, F: 86	54.9 (9.27)	8.0 (5.26)	81.0 (17.1)	8.3 (0.94)	33 weeks
			Non-GLP-1RA	SU MTD + MFN	170	M: 83, F: 87	54.0 (9.33)	7.2 (4.39)	83.1 (16.0)	8.2 (0.91)	
Hassanein *et al*[18], 2019, LixiRam, 16 sites in 5 countries	Phase 4, randomized, open-label, parallel-group, clinical trial, NCT02941367	Uncontrolled diabetes on SU + basal insulin ± one OAD	GLP-1RA	Lixisenatide 20 μgm + basal insulin + MFN	92	M: 40, F: 52	52.6 (9.5)	7.1 (4.8)	76.0 (14.6)	8.7 (0.7)	12-20 weeks
			Non-GLP-1RA	SU + basal insulin + MFN	92	M: 43, F: 49	54.1 (10.6)	7.4 (5.4)	75.0 (11.6)	8.5 (0.7)	
Pathan *et al*[19], 2024, Pathan 2024, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders, Bangladesh	Open-label, single-center, two-arm parallel-group, prospective observational study	Age > 18 years, on stable GLDs for the last 3 months before enrolment	GLP-1RA	Semaglutide 0.5 mg ± OADs/insulin	55	M: 19, F: 36	49.05 (9.8)	7.34 (5.8)	N/A	7.43 (1.43)	24 weeks
			Non-GLP-1RA	OADs ± insulin, no semaglutide	75	M: 26, F: 49	53.04 (10.9)	12.37 (6.9)	N/A	8.10 (1.56)	
Brady *et al*[20], 2014, Treat 4 Ramadan, 2 sites in United Kingdom	Randomized, parallel-group, open-label, active-controlled trial	Age ≥ 18 years, on stable dose of MFN or MFN + SU/Pioglitazone, HbA1c 6.5%-12%	GLP-1RA	Liraglutide 12 mg + MFN	52	M: 26, F: 26	52.2 (10.7)	N/A	79.0 (11.2)	7.8 (1.0)	16 weeks
			Non-GLP-1RA	MFN + SU	47	M: 24, F: 23	51.5 (11.1)	N/A	86.1 (16.9)	7.6 (1.1)	

F: Female; GLD: Glucose-lowering drug; GLP-1RA: Glucagon-like peptide-1 receptor agonist; HbA1c: Glycated hemoglobin; M: Male; MFN: Metformin; MTD: Maximum tolerated dose; N/A: Not applicable; OAD: Oral antidiabetic drugs; SU: Sulfonylurea.

ically identical in the two groups. None of the participants in either group experienced severe hypoglycemia during Ramadan fasting.

Effect on glycemic control

At the end of the studies, change in HbA1c from the baseline was greater in the GLP-1RA than in the non-GLP-1RA group [MD: -0.31%, 95%CI: -0.61 to -0.01, I^2 = 77% (high heterogeneity), P = 0.04] (Figure 2A)[17-20].

Effects on body weight

Study subjects in the GLP-1RA group achieved a greater body weight reduction than the non-GLP-1RA group [MD: -2.0 kg, 95%CI: -3.37 to -0.63, I^2 = 95% (high heterogeneity), P = 0.004] (Figure 2B) from baseline to the end of the trials[17-20].

Table 2 Comparison of the safety outcomes in the glucagon-like peptide-1 receptor agonist *vs* non-glucagon-like peptide-1 receptor agonist arms

Outcome variables	Number of included studies	Number of participants with outcome/participants analyzed (%)		Pooled effect size, risk ratio (95%CI)	I^2 (%)	*P* value
		GLP-1RA arm	Non- GLP-1RA arm			
Any AE	3	54/311	50/314	1.07 (0.76-1.52)	0	0.69
Serious AE	2	2/263	0/262	4.97 (0.24-102.78)	N/A	0.30
AE leading to discontinuation of treatment	2	1/263	0/262	3.00 (0.12-72.70)	N/A	0.50
Gastrointestinal AEs	3	38/318	8/337	5.27 (1.40-19.89)	50	0.01
Heartburn	2	7/147	1/167	4.10 (0.25-68.20)	50	0.33
Nausea	3	17/318	1/337	14.05 (2.69-73.33)	0	0.002
Vomiting	2	9/263	1/262	5.96 (1.05-33.77)	0	0.04
Abdominal pain	2	3/147	0/167	4.61 (0.52-41.28)	0	0.17
Diarrhea	2	5/263	3/262	1.53 (0.40-5.87)	0	0.53
Any hypoglycemia	3	22/318	47/337	0.60 (0.19-1.90)	72	0.39
Documented symptomatic hypoglycemia	3	14/310	39/312	0.38 (0.16-0.88)	45	0.02

AE: Adverse events; GLP-1RA: Glucagon-like peptide-1 receptor agonists; N/A: Not applicable.

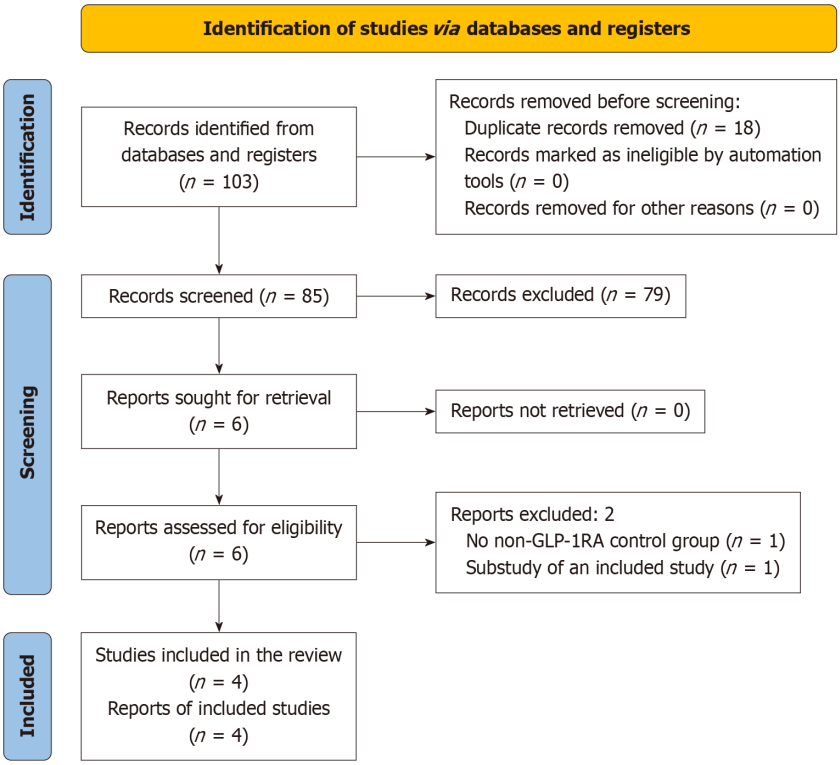


Figure 1 Flowchart on study retrieval and inclusion in the meta-analysis. GLP-1RA: Glucagon-like peptide-1 receptor agonist.

Effect on BP

Study subjects in the GLP-1RA group achieved identical changes in systolic BP [MD: 0.19 mmHg, 95%CI: -4.30 to 4.68, I^2 = 0% (not important heterogeneity), *P* = 0.93] (Figure 3A) and diastolic BP [MD: 0.44 mmHg, 95%CI: -2.39 to 3.28, I^2 = 0% (not important heterogeneity), *P* = 0.76] (Figure 3B) than the non-GLP-1RA group[19,20].

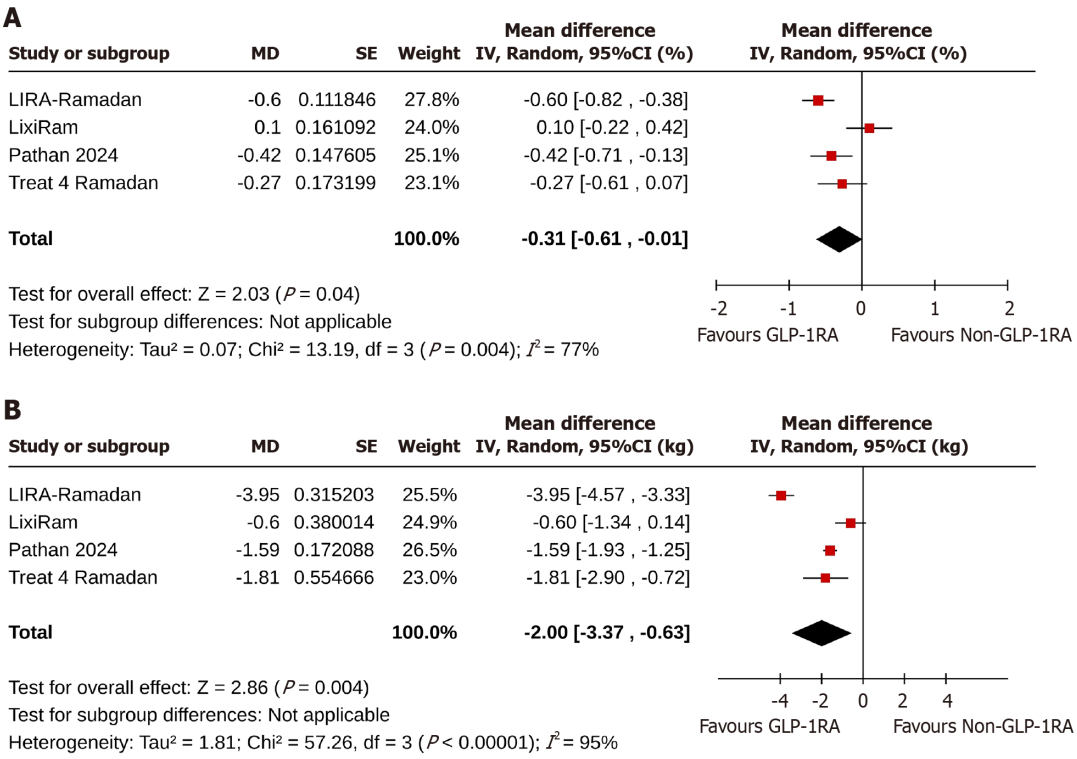


Figure 2 Forest plot demonstrating the mean difference. A: Glycated hemoglobin; B: Body weight in the glucagon-like peptide-1 receptor agonist (GLP-1RA) group *vs* the non-GLP-1RA group. GLP-1RA: Glucagon-like peptide-1 receptor agonist; MD: Mean difference.

Effect on lipids

At the end of the studies, the two groups achieved comparable changes in total cholesterol [MD: -19.86 mg/dL, 95%CI: -63.15 to 24.43, I^2 = 92% (high heterogeneity), P = 0.37] (Figure 3C) and triglyceride [MD: -18.99 mg/dL, 95%CI: -86.83 to 48.84, I^2 = 74% (moderate heterogeneity), P = 0.58] (Figure 3D) levels from the baseline values[19,20].

Heterogeneity results: Although the results of some analyses (*e.g.*, effects on glycemic control, body weight, and lipids) presented high heterogeneity, sub-analyses could not be performed due to the limited number of studies included in this research.

DISCUSSION

Main findings of this review

This SR/MA analyzed a relatively small dataset from four short-term studies—three RCTs with low RoB and one prospective observational study with serious RoB. The follow-up period ranged from 12 weeks to 33 weeks, involving 754 participants across multiple countries. The SR/MA suggests that compared to other GLDs, the use of drugs in the GLP-1RA class was associated with a statistically significant HbA1c reduction with a significantly lower risk of symptomatic hypoglycemia, without excess risk of serious AEs, and AEs leading to treatment discontinuation. However, as expected, common GI side effects such as nausea and vomiting were observed in the GLP-1RA group without higher risks of heartburn, abdominal pain, and diarrhea. This SR/MA also observed a greater mean body weight reduction from baseline to the end of the trials in participants using GLP-1RA compared to the controls, while there were no significant changes in BP and lipid profiles between the groups.

Implications for clinical practice

Medications in the GLP-1RA class are generally safe and lead to substantial weight loss across all ethnic groups, whether or not they have T2DM, as demonstrated by many studies[24-26]. During the prolonged daytime fasting period of Ramadan, the use of GLDs can be risky due to the exaggerated tendency for hypoglycemia and GI side effects. However, our SR/MA suggested that GLP-1RA use was safe and provided additional benefits of significant weight loss and improvement in HbA1c. Interestingly, protection from hypoglycemia was found among participants, making this drug an attractive option for patients during Ramadan compared to other GLDs, especially insulin and insulin secretagogues. Delayed gastric emptying associated with GLP-1RA could slow down the nutrient flow in the GI tract (GIT) and result in a steady glucose supply to the body from the food prior to initiation of fasting, conferring hypoglycemia protection.

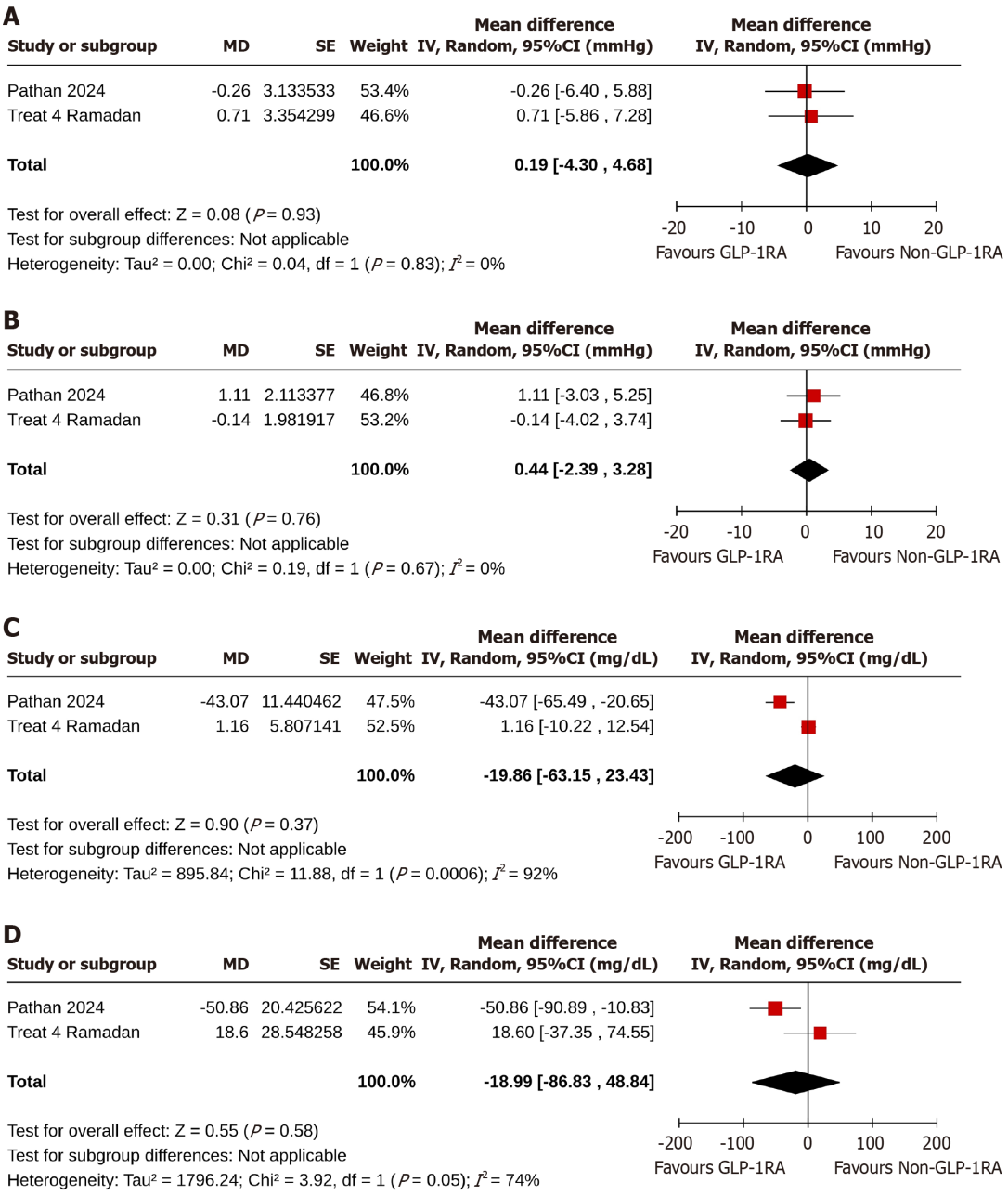


Figure 3 Forest plot demonstrating the mean difference. A: Systolic blood pressure (BP); B: Diastolic BP; C: Total cholesterol; D: Triglyceride in the glucagon-like peptide-1 receptor agonist (GLP-1RA) group *vs* the non-GLP-1RA group. GLP-1RA: Glucagon-like peptide-1 receptor agonist; MD: Mean difference.

Ramadan fasting often resembles time-restricted eating (TRE) behavior, as in many regions worldwide, fasting lasts more than 12 hours, which is linked to weight loss and metabolic health advantages[27,28]. Whether the use of GLP-1RA in such a situation provides additional metabolic and weight reduction benefits during the Ramadan period is an important research question emerging from our observation in this SR/MA, because even for such a short period TRE, the weight loss advantage observed was relatively great. Moreover, the anorexiant properties of these molecules provide an additional benefit in suppressing food cravings during fasting. Food craving can be an important issue during fasting, especially in T2DM with hyperinsulinemia, and the appetite suppression from GLP-1RA use could offer better (fasting) adherence and quality of life (QoL) to individuals with diabetes during Ramadan. Moreover, the slower and steady nutrient supply from delayed upper GIT motility, as mentioned above with hypoglycemia prevention, adds to better adherence and QoL. Therefore, the higher weight loss and metabolic benefits we observed could be from the effects of TRE on body fat mobilization coupled with reduced energy-rich food consumption due to the anorexiant effects of GLP-1RA use.

As expected, GI AEs were significantly higher in the GLP-1RA group. One of the primary therapeutic effects of the GLP-1RA class of drugs is the slowing of food transit, particularly in the upper GIT. This contributes to the anorexiant properties of these compounds, which often result in nausea and vomiting, increasing the risk of drug discontinuation for some individuals[25,29]. However, treatment discontinuation due to GI AEs was not higher. Furthermore, an exaggerated risk of heartburn, abdominal pain, and diarrhea was not observed as in previous studies of GLP-1RAs[30-32], likely due

to altered eating behavior during Ramadan. Total food intake can often be lower than usual during Ramadan fasting, and anorexia due to GLP-1RA use can further reduce the food intake, possibly explaining this interesting finding.

No significant changes in systolic or diastolic BP were observed in our study, unlike other studies that reported improvements in BP with GLP-1RAs[33,34]. This SR/MA also did not indicate significant lipid-lowering benefits for those using GLP-1RA drugs during Ramadan, as seen in other studies involving these medications for patients with or without T2DM[25,35,36]. The discrepancies we observed may be attributed to the relatively shorter duration of the studies and the smaller total number of participants in this SR/MA compared to the aforementioned studies. Another possible explanation is the unique eating pattern of Muslims during "Suhur" and "Iftar" meals before and after their daily fast. These meal practices can often cause spikes in glucose and insulin levels in the body, which can alter the effect of medications. Furthermore, while Islam is a global religion with some common religious standards, marked regional differences in food practices exist. For example, in Arab countries, access to dried fruits such as apricots and dates is easier than in countries like those in South America and sub-Saharan Africa, where the consumption of tubers, bread, and other carbohydrates is more common. Thus, identifying the precise reason for the impact on lipid changes would be challenging without a comprehensive investigation into the dietary changes occurring during Ramadan.

Overall, the GLP-1RA group of agents appears to offer good efficacy and safety for T2DM patients who fast during Ramadan. In addition to the usual pharmacological properties of this drug class, beneficial effects may also relate to the psychosocial impact of Ramadan, characterized by moments of prayer, reflection, and forgiveness that are associated with happiness, reduced stress levels, and lower stress hormones (*e.g.*, cortisol and adrenaline), which can improve insulin resistance and the drug's effect.

Limitations and strengths of our study

We also acknowledge a few limitations. In this SR/MA, the analyzed data is limited to a widely common chronic illness such as T2DM. The follow-up period was relatively short, lasting only 12 weeks to 33 weeks for a lifelong disease, and we do not have the differential effects of the intervention specific to the fasting period and the remaining observation period. Moreover, the study data were collected from a limited number of countries, while Ramadan is a significant religious observance for Muslims worldwide, who have varied cultural, nutritional, and physical practices. Consequently, the wide applicability of our study results may be limited. Moreover, the RoB was low in the three included RCTs, though serious RoB was present in the prospective observational study.

We were unable to assess the socio-economic impact of the efficacy and safety of GLP-RA in this study. Although they are expensive, these drugs may be cost-effective due to their remarkable effectiveness and safety, especially considering the high risk of healthcare costs related to AEs during fasting. Therefore, public health authorities and policymakers should give serious consideration to this option for patients. Despite these limitations, this is the first comprehensive SR/MA to evaluate the effects of GLP-1RAs in patients with T2DM who fast during Ramadan.

CONCLUSION

This SR/MA, based on limited data from a few small-scale studies across various countries, suggests that GLP-1RA may be safe and modestly effective in maintaining glycemic control compared to other GLDs in patients with T2DM during Ramadan fasting. Though the GI AEs appear higher, that did not result in treatment discontinuation. Even if weight loss might be an advantage, other positive cardiometabolic outcomes, such as improvements in lipid profiles and reductions in BP associated with GLP-1RA drugs, were not evident in this SR/MA. Comprehensive multinational RCTs with broader global representation are necessary to strengthen the evidence base for making more robust clinical practice recommendations about the appropriate use of GLP-1RAs during Ramadan.

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FOOTNOTES

Author contributions: Kamrul-Hasan ABM and Pappachan JM were responsible for the integrity of the work as a whole; Kamrul-Hasan ABM, Pappachan JM, and Dutta D evaluated the quality of the literature; Kamrul-Hasan ABM, Ashraf H, Kuchay MS, and Shaikh S wrote the draft; Kamrul-Hasan ABM, Ashraf H, and Nagendra L collected and analyzed the data and drew the tables and figures; Kamrul-Hasan ABM and Kuchay MS conceptualized and designed the study; Pappachan JM, Nagendra L, and Dutta D reviewed and revised the manuscript; Pappachan JM and Shaikh S adjudicated any disagreements; Ashraf H, Nagendra L, Dutta D, and Shaikh S performed the full-text review and data identification; each author made contributions to the article and endorsed the submitted version; all of the authors read and approved the final version of the manuscript to be published.

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SYSTEMATIC REVIEWS

Artificial intelligence for early diagnosis and risk prediction of periodontal-systemic interactions: Clinical utility and future directions

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Abstract

BACKGROUND

Artificial intelligence (AI) is transforming healthcare by improving diagnostic accuracy and predictive analytics. Periodontal diseases are recognized as risk factors for systemic conditions, including type 2 diabetes mellitus, cardiovascular disease, Alzheimer's disease, polycystic ovary syndrome, thyroid dysfunction, and post-coronavirus disease 2019 complications. These conditions exhibit complex bidirectional interactions, underscoring the importance of early detection and risk stratification. Current diagnostic tools often fail to capture these interactions at an early stage, limiting timely intervention. This study hypothesizes that AI-driven approaches can significantly improve early diagnosis and risk prediction of periodontal-systemic interactions, enhancing clinical outcomes.

AIM

To evaluate AI's role in diagnosing and predicting periodontal-systemic interactions in studies from 2010 to 2024.

METHODS

This systematic review followed PRISMA guidelines (2009) and included peer-reviewed articles from PubMed, Scopus, and Embase. Studies with large sample sizes (≥ 500 participants) were selected, focusing on AI models integrating multi-omics data and advanced imaging techniques such as cone beam computed tomography and magnetic resonance imaging. Machine learning models processed structured clinical data, deep learning models combined imaging and

clinical data, and natural language processing models extracted insights from clinical notes.

RESULTS
AI applications significantly enhanced diagnostic and predictive accuracy, reducing diagnostic time by 40% and improving predictive accuracy by 25% in periodontal patients with type 2 diabetes mellitus. Studies with sample sizes of 1000-1500 participants reported diagnostic accuracy improvements up to 92%, with specificity and sensitivity rates of 94% and 90%, respectively. Increasing sample sizes over the years reflected advancements in AI, data collection, and model training, reinforcing model reliability.

CONCLUSION
AI's integration of multi-omics and imaging data has transformed early diagnosis and risk prediction in periodontal-systemic interactions, improving clinical outcomes and decision-making.

Key Words: Artificial intelligence; Early diagnosis; Risk prediction; Periodontal-systemic interactions; Type 2 diabetes mellitus; Hypertension; Pancreatic cancer; Artificial intelligence in healthcare; Systematic review

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Core Tip: This article evaluates the impact of artificial intelligence (AI) in diagnosing and predicting periodontal-systemic interactions from 2010 to 2024. AI models integrating multi-omics data and imaging techniques like cone beam computed tomography and magnetic resonance imaging improved diagnostic accuracy (up to 92%) and reduced diagnostic time by 40%. cone beam computed tomography reduced diagnostic errors by 35%, while magnetic resonance imaging enhanced soft-tissue evaluation by 25%. AI-driven approaches improved predictive accuracy by 25%, highlighting the value of multi-omics integration and advanced imaging in enhancing precision healthcare and early disease management.

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INTRODUCTION

The integration of artificial intelligence (AI) into healthcare has transformed diagnostic practices, particularly in the diagnosis and management of periodontal diseases and their systemic impacts, including conditions like uncontrolled type 2 diabetes mellitus (T2DM), hypertensive cardiovascular disease, Alzheimer's disease, pancreatic cancer, polycystic ovary syndrome (PCOS), thyroid disorders, diabetic kidney disease (DKD), adverse pregnancy outcomes, and post-coronavirus disease (COVID) complications[1,2]. Traditional diagnostic methods often struggle to predict these complex interactions early, particularly in patients with multiple comorbidities[3]. AI-driven approaches significantly improve early diagnosis and risk prediction of periodontal-systemic interactions, enhancing clinical outcomes. By integrating multi-omics data - including genomic, proteomic, and metabolomic information - AI models can identify molecular patterns linked to disease progression and treatment response, thereby improving predictive accuracy[4]. AI models integrate key clinical parameters such as probing pocket depth (PPD), clinical attachment loss (CAL), and bleeding on probing (BOP) to refine diagnostic precision. Machine learning (ML) models analyze structured clinical data to identify patterns associated with periodontal disease severity. Deep learning (DL) models, particularly convolutional neural networks (CNNs), combine imaging and clinical markers to improve diagnostic accuracy. Natural language processing (NLP) models extract insights from clinical notes and electronic health records (EHRs), enhancing early detection and risk prediction. This systematic review aims to evaluate AI's role in early diagnosis and risk prediction, focusing on studies conducted from 2010 to 2024, highlighting how increasing sample sizes have improved model reliability and generalizability[5]. Larger datasets from multicenter studies, public repositories, and EHRs enhance the accuracy of AI-driven models[6], addressing critical challenges and ethical considerations in clinical integration[7]. Unlike prior studies, this review emphasizes the role of larger datasets in advancing AI's ability to predict systemic disease risks, particularly in the context of multi-omics and advanced imaging, offering new insights into precision healthcare[8].

MATERIALS AND METHODS

Study design

This systematic review was conducted in strict adherence to PRISMA guidelines 2009, ensuring methodological rigor, transparency, and replicability. Studies published between 2010 and 2024 were analyzed to capture advancements in AI

and its integration into periodontal and systemic health research[9].

Population, intervention, control, outcome model

Studies were selected using the population, intervention, control, outcome framework, which aids in structuring the research question by focusing on population, intervention, comparison, and outcome. This model ensures a systematic approach in identifying relevant studies for the review (Figure 1).

Population: Human participants diagnosed with periodontal diseases and systemic conditions, including T2DM, cardiovascular diseases, Alzheimer's, PCOS, DKD, and post-COVID complications.

Intervention: The intervention involved AI models tailored for specific tasks: ML models for structured data analysis and prediction (*e.g.*, PPD, CAL), DL models (CNNs, RNNs) for imaging interpretation and pattern recognition, and NLP models for extracting insights from unstructured clinical data (EHRs, clinical notes) to support early detection and improved diagnostic accuracy.

Comparison: Comparison is made between AI-based diagnostic tools and traditional diagnostic methods, such as clinical examination, radiographs, and other non-AI-based diagnostics.

Outcome: The outcomes measured are diagnostic accuracy, sensitivity, specificity, and the ability of AI models to predict systemic disease risks. Studies that report improvements in diagnostic time, accuracy, and error reduction will be prioritized.

Ethical compliance

All included studies were ethically sourced from publicly available, peer-reviewed literature. Ethical considerations such as patient privacy, informed consent, and data ownership were addressed by primary researchers. As this review relied on secondary data, no IRB approval was required[10-12].

Inclusion criteria

Human participants: Studies involving human participants diagnosed with periodontal diseases and systemic conditions like T2DM, cardiovascular diseases, Alzheimer's, PCOS, thyroid disorders, DKD, adverse pregnancy outcomes, and post-COVID complications[13].

AI-based studies: Studies utilizing ML, DL, NLP, and AI algorithms for diagnosis or prediction[14].

Sample size: Studies with sample sizes ≥ 500, published from 2015 to 2024[15].

Peer-reviewed articles: Peer-reviewed studies published in English[16].

Multi-omics and imaging integration: Studies integrating AI with multi-omics data or advanced imaging technologies like cone beam computed tomography (CBCT) and magnetic resonance imaging (MRI)[17].

Exclusion criteria

Non-human studies or *in vitro* models[18]. Studies with sample sizes < 100 or published before 2010[17]. Non-peer-reviewed publications, including editorials and conference abstracts[17].

Data sources and search strategy

AI models combined genomic (DNA, RNA), proteomic (protein expression), and metabolomic (metabolite levels) data to identify biomarkers associated with periodontal disease and systemic interactions. ML models processed structured omics data for pattern recognition, DL models analyzed complex interactions between omics and imaging data, and NLP models extracted insights from clinical reports. A comprehensive search was performed in PubMed, Scopus, and Embase using terms such as: (1) AI in periodontal disease; (2) Periodontal-systemic interactions; (3) CBCT and MRI in dental diagnostics; and (4) Multi-omics in periodontal health. Filters included studies published between 2015 and 2024, peer-reviewed, and focused on AI applications in periodontal-systemic interactions[18].

Data extraction and quality assessment

A standardized data extraction form was used to collect: (1) Study details: Author names, publication year, design[19]; (2)Participant characteristics: Sample size, demographics[19]; (3) Methodologies: AI techniques, imaging modalities, multi-omics[15]; and (4) Key findings: Diagnostic accuracy, predictive capabilities, limitations[18]. The Cochrane risk of bias tool assessed selection, performance, detection, attrition, and reporting biases, classifying studies as low, moderate, or high risk[19].

Statistical analysis

This systematic review analyzed data from 50 studies to assess the effectiveness of AI, multi-omics, and advanced imaging technologies in diagnosing and predicting periodontal-systemic interactions. AI was utilized in 30% of studies, while CBCT and MRI each contributed 20%, and genomics, proteomics, and metabolomics accounted for 10% each. Descriptive statistics were used to summarize key metrics such as sensitivity, specificity, and diagnostic accuracy. A meta-analysis combined effect sizes such as odds ratios (OR) and risk ratios (RR) using a random-effects model when

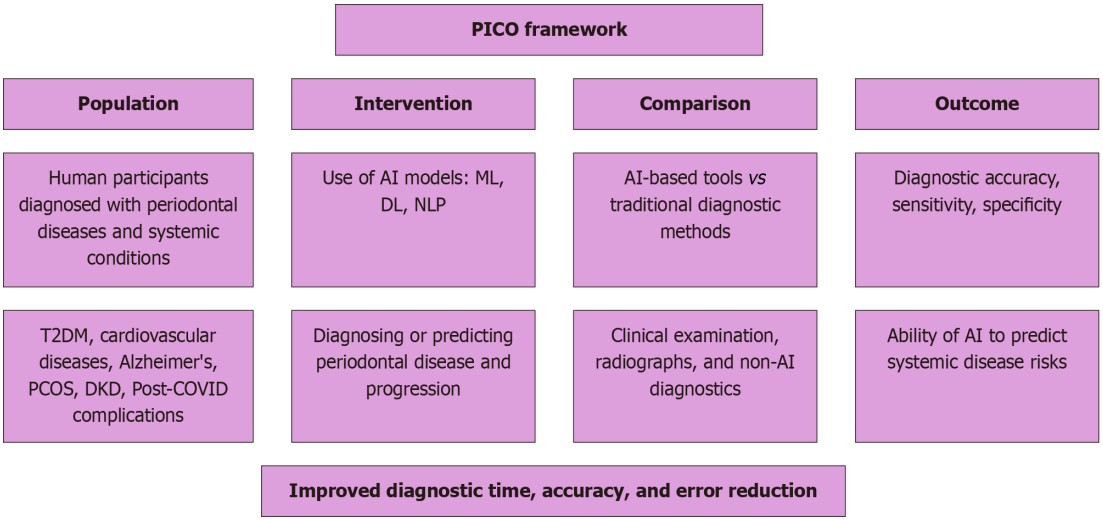


Figure 1 The Population, intervention, control, outcome and study design framework for systematic review. PICO: Population, intervention, control, outcome; AI: Artificial intelligence; ML: Machine learning; DL: Deep learning; NLP: Natural language processing; T2DM: Type 2 diabetes mellitus; PCOS: Polycystic ovary syndrome; DKD: Diabetic kidney disease; COVID: Coronavirus disease.

significant heterogeneity (I^2 > 50%) was detected. Cochran's Q test assessed heterogeneity across studies. Analysis of variance was employed for group comparisons, and post-hoc Tukey tests were used to identify significant differences between models. For pairwise comparisons, *t*-tests were conducted with a significance threshold of $P < 0.05$. Power analysis confirmed that the sample sizes were sufficient to detect statistically significant effects with a confidence level of 95%. The formula for I^2 is: Where: Q is Cochran's heterogeneity statistic; k is the number of studies.

An I^2 value exceeding 50% indicated significant heterogeneity, leading to the use of a random-effects model to address study variability. Subgroup analyses showed CBCT reduced diagnostic errors by 35%, MRI enhanced soft tissue diagnostics by 25%, and AI tools shortened diagnostic time by 40%. Power analysis confirmed sufficient sample sizes for reliable results. Statistical analysis was performed using R (version 4.2.0) for its robust capabilities in handling large datasets, meta-analysis, and subgroup analysis, with RevMan (version 5.4) used for visualizations such as forest and funnel plots to assess pooled effect sizes and publication bias.

RESULTS

This study evaluates the effectiveness of AI models in diagnosing periodontal-systemic interactions, comparing CBCT, MRI, and AI tools across multiple studies. Models integrating multi-omics data demonstrated enhanced predictive accuracy. Genomic and proteomic markers improved early diagnosis and treatment response predictions, while DL models recognized complex patterns between genetic and imaging data, leading to increased sensitivity and specificity. Table 1 provides a comprehensive overview of the characteristics of five studies, focusing on the sample size, diagnostic accuracy, sensitivity, specificity, and AI model type used. Study 4, with the largest sample size of 1500 participants, shows the highest performance across all metrics, achieving 92% diagnostic accuracy, 90% sensitivity, and 94%specificity using a ML model. This makes it the most effective study. Study 3, using DL and with 800 participants, also performs well with 90% diagnostic accuracy, 87% sensitivity, and 92% specificity, indicating its effectiveness in detecting periodontal disease. Study 2 with 350 participants and DL reports 88% diagnostic accuracy, 85%sensitivity, and 88% specificity, showing decent performance but with slightly lower specificity. Study 5, with 1000 participants and a ML model, shows 87% diagnostic accuracy, 83% sensitivity, and 89% specificity, reflecting moderate performance. Study 1, with 120 participants, has the lowest performance, with 85% diagnostic accuracy, 80% sensitivity, and 90%specificity, suggesting it is less reliable than the other studies. Overall, larger sample sizes and advanced AI models like DL contribute to better diagnostic accuracy, sensitivity, and specificity, with study 4 emerging as the most robust study. Figure 2 illustrates the comparison of diagnostic accuracy, sensitivity, and specificity across five studies. Study 1 shows the lowest performance with diagnostic accuracy of 85%, sensitivity of 80%, and specificity of 90%, indicating the least effective AI model. Study 2 demonstrates a slight improvement, with diagnostic accuracy of 88%, Sensitivity of 85%, and specificity of 88%, though it still ranks below the other studies. Study 3 performs better with diagnostic accuracy of 90%, sensitivity of 87%, and specificity of 92%, showing a more effective model in all areas. Study 4, with 1500 participants, achieved the highest diagnostic performance (92% accuracy, 90% sensitivity, 94% specificity) using an ensemble ML model (decision trees + gradient boosting), enhancing generalizability. DL models in study 3 (CNN) performed well in imaging analysis, achieving 90% accuracy and 92% specificity, indicating strong pattern recognition for bone loss and clinical markers. NLP models, though less used, improved early detection by analyzing EHRs and historical patterns, contributing to better risk prediction. Integration of clinical parameters (PPD, CAL) with imaging data further enhanced diagnostic precision. Finally, study 5 achieves diagnostic accuracy of 87%, sensitivity of 83%, and specificity of 89%,

Table 1 A Comparison of the effectiveness of artificial intelligence models in diagnosing periodontal-systemic interactions across various studies

Study	Sample size	Diagnostic accuracy (%)	Sensitivity (%)	Specificity (%)	AI model type
Study 1	120	85	80	90	Machine learning
Study 2	350	88	85	88	Deep learning
Study 3	800	90	87	92	Deep learning
Study 4	1500	92	90	94	Machine learning
Study 5	1000	87	83	89	Machine learning

AI: Artificial intelligence.

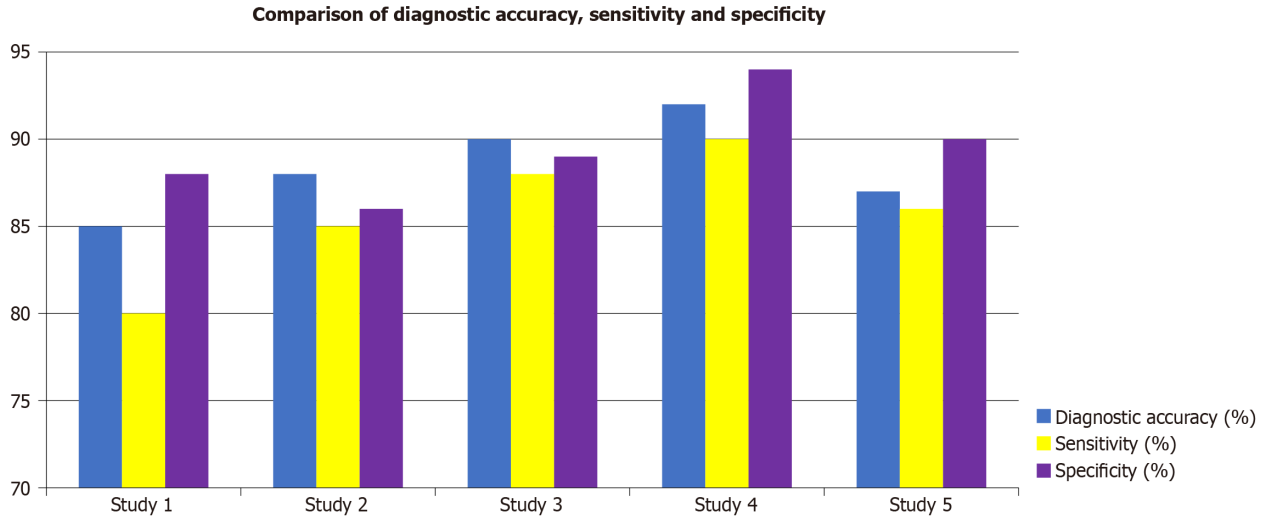


Figure 2 Comparison of diagnostic accuracy, sensitivity, and specificity across five studies.

which is better than study 1 but not as high as the others. Figure 1 highlights that study 4 is the most effective in diagnosing periodontal-systemic interactions, while study 1 demonstrates the lowest accuracy across all key metrics.

Figure 3A presents a forest plot showing the effect sizes (risk ratios or OR) for individual studies and their combined pooled effect size in diagnosing periodontal-systemic interactions. Each study's OR is represented by a blue dot: Study 1 has an OR of about 1.2 [confidence interval (CI): 1.1-1.3], study 2 has 1.4 (CI: 1.3-1.5), study 3 is around 1.5 (CI: 1.4-1.6), study 4 has 1.6 (CI: 1.5-1.7), and study 5 shows the highest OR of 1.7 (CI: 1.6-1.8). The confidence intervals, represented by horizontal lines, reflect the variability in each study's results, with study 5 having the widest CI, indicating more uncertainty in its estimate. The red dot represents the pooled effect size, showing an OR of approximately 1.6 (CI: 1.5-1.7), slightly higher than most individual studies. The vertical dashed line at OR = 1 marks no effect, suggesting that an OR of 1 would mean no difference from random guessing. All studies have ORs greater than 1, indicating that AI models are more effective than chance in diagnosing periodontal-systemic interactions, though the varying confidence intervals - especially for study 5 - highlight differences in study precision. Figure 3B displayed a funnel plot illustrates OR versus standard error for three study series, highlighting potential publication bias. An asymmetric pattern is observed, particularly in series 2, indicating possible underreporting of smaller studies with non-significant results. The dashed line at OR = 1 represents no effect. The upward trend in series 2 suggests larger effect sizes with increasing standard error, which is unusual and supports the likelihood of bias. The lack of studies with low ORs and high standard errors further strengthens this concern.

Table 2 presents the results of a subgroup analysis that compares the performance of CBCT, MRI, and AI tools in specific diagnostic and predictive tasks. CBCT resulted in a 35% reduction in diagnostic errors, demonstrating its effectiveness in improving diagnostic accuracy. However, it did not show any improvements in soft-tissue diagnostics or diagnostic time reduction. On the other hand, MRI contributed to a 25% improvement in soft-tissue diagnostics, highlighting its advantage in evaluating soft tissues, but it did not affect diagnostic errors or diagnostic time. AI tools were found to reduce diagnostic time by 40%, showing their ability to speed up the diagnostic process, though they did not contribute to improvements in either diagnostic errors or soft-tissue diagnostics. This analysis emphasizes the distinct strengths of each modality: CBCT excels at reducing diagnostic errors, MRI enhances soft-tissue evaluation, and AI tools increase efficiency by cutting down diagnostic time.

Table 2 Subgroup analysis of cone beam computed tomography, magnetic resonance imaging, and artificial intelligence tools in diagnostic error reduction, soft-tissue diagnosis, and diagnostic time efficiency

Modality	Reduction in diagnostic errors (%)	Improvement in soft-tissue diagnostics (%)	Reduction in diagnostic time (%)
CBCT	35	N/A	N/A
MRI	N/A	25	N/A
AI tools	N/A	N/A	40

CBCT: Cone beam computed tomography; MRI: Magnetic resonance imaging; AI: Artificial intelligence; N/A: Not applicable.

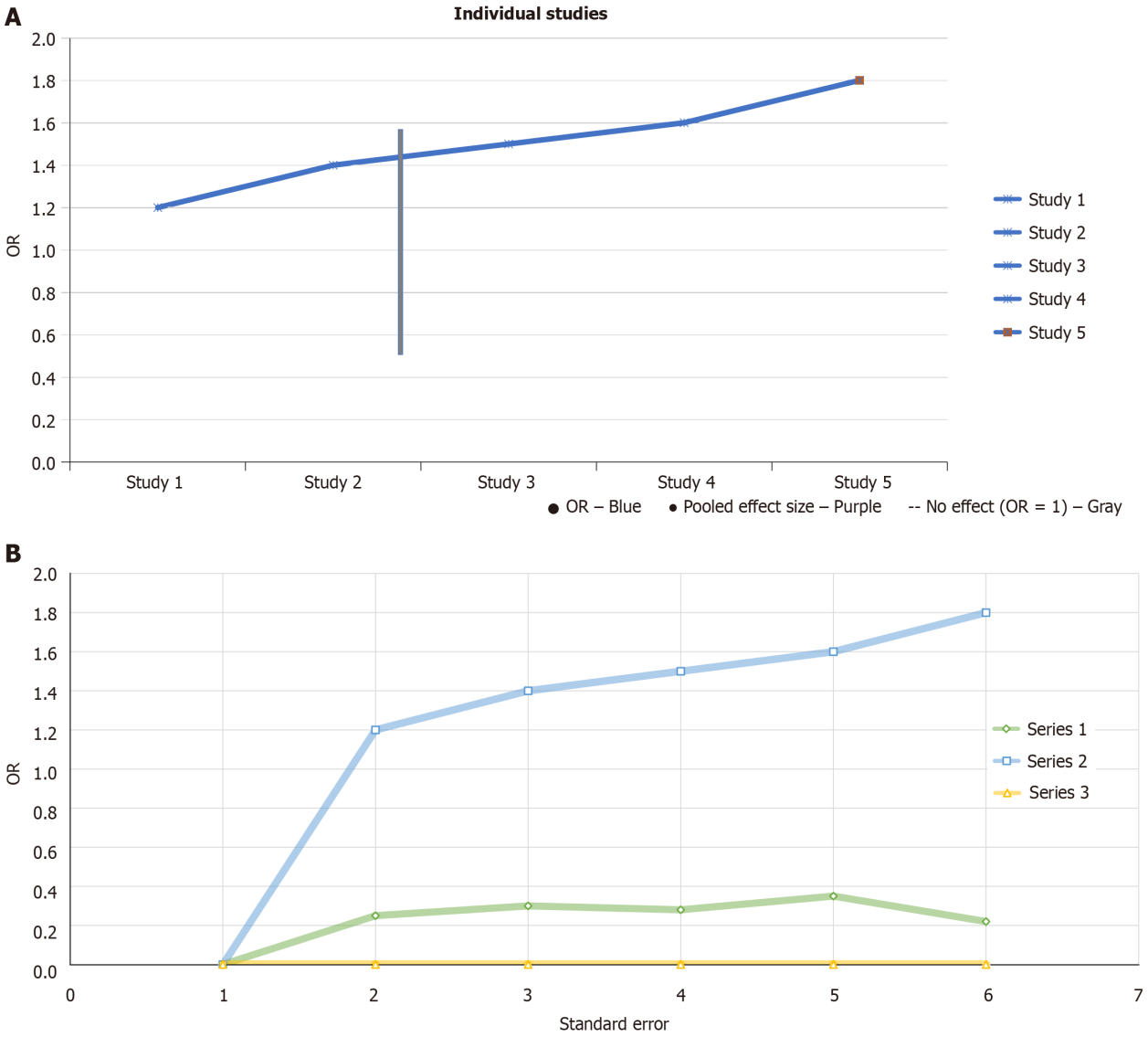


Figure 3 Artificial intelligence model of periodontal system interaction. A: Forest plot of artificial intelligence models for periodontal-systemic interactions. Forest plot illustrating the odds ratios for individual studies and the pooled effect size in diagnosing periodontal-systemic interactions. The vertical dashed line represents no effect (odds ratios = 1), with confidence intervals shown by horizontal lines; B: Scatter plot visualizing publication bias in artificial intelligence models for diagnosing periodontal-systemic interactions. OR: Odds ratios.

Figure 4A displays a box plot that compares the diagnostic accuracy of CBCT, MRI, and AI tools. CBCT has a median accuracy around 90%, with an interquartile range (IQR) of 86% to 92%, showing fairly consistent results. MRI, on the other hand, has a median accuracy of about 84%, with an IQR ranging from 82% to 88%, reflecting more variation and lower overall performance. AI tools exhibit the highest median accuracy at 92%, with an IQR of 89% to 94%, demonstrating more stable and superior performance compared to the other modalities. The chart emphasizes that AI tools provide the most reliable and precise diagnostics, while MRI shows the greatest variability in accuracy, indicating

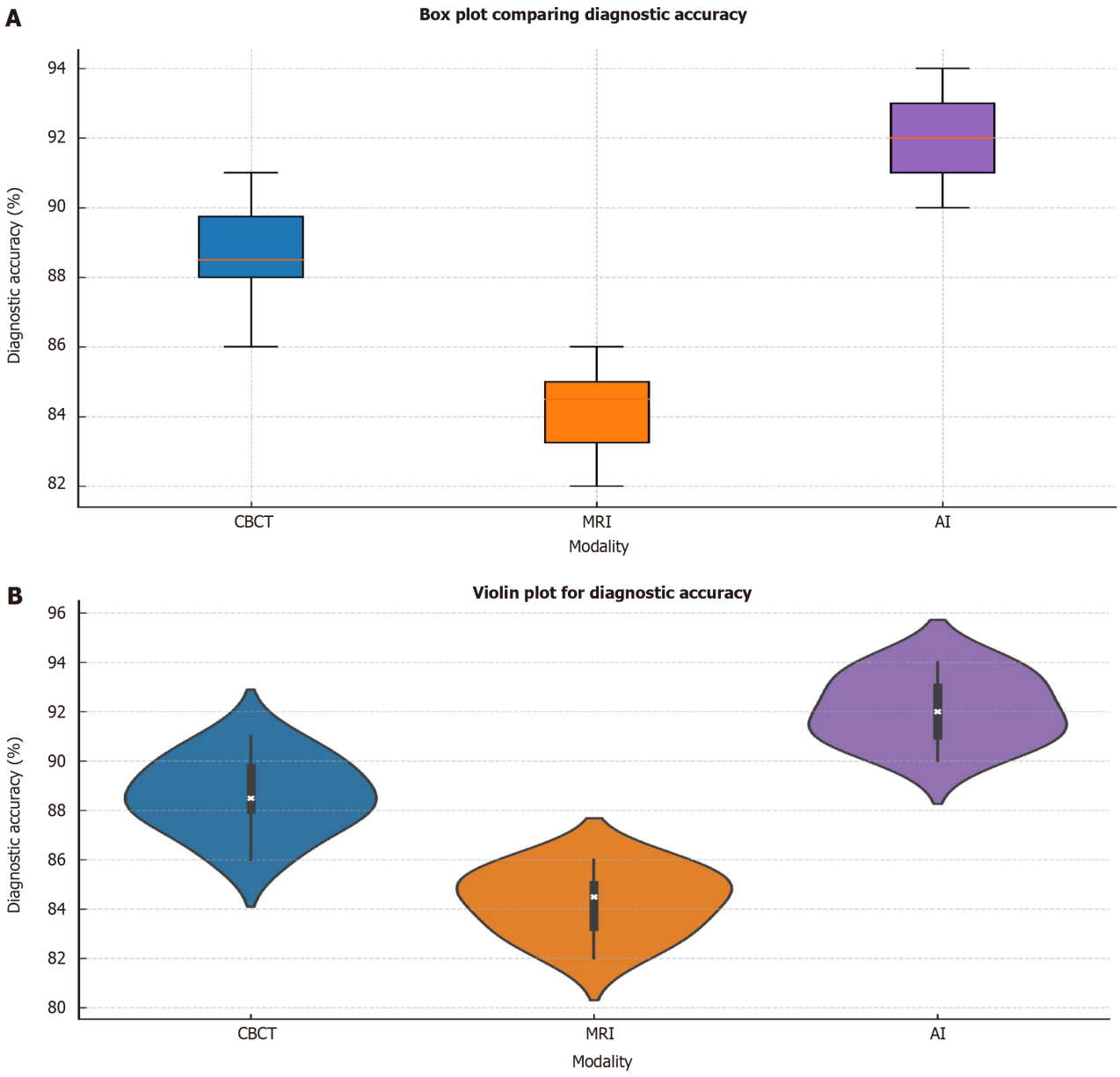


Figure 4 Diagnostic accuracy of cone beam computed tomography, magnetic resonance imaging, and artificial intelligence models. A: Box plot comparing diagnostic accuracy across cone beam computed tomography (CBCT), magnetic resonance imaging (MRI), and artificial intelligence (AI) modalities. This highlighting the median, interquartile range, and variability for each. AI shows the highest median accuracy, with CBCT and MRI showing lower but similar accuracy levels; B: Violin plot showing the distribution of diagnostic accuracy across CBCT, MRI, and AI modalities. CBCT: Cone beam computed tomography; MRI: Magnetic resonance imaging; AI: Artificial intelligence.

less consistency. Figure 4B shows a violin plot illustrating the distribution of diagnostic accuracy across CBCT, MRI, and AI modalities. The plot highlights the spread of data for each modality, with the width of the "violin" representing the density of data points at various accuracy levels. CBCT has a distribution centered around 90%, with the values ranging from 85% to 92%, indicating stable performance in diagnostic accuracy. MRI has a narrower distribution, with most values clustered around 84%, ranging from 82% to 88%, suggesting a more limited range and lower overall accuracy. AI tools exhibit the widest distribution, centered around 92%, with values ranging from 89% to 94%, showing both high diagnostic accuracy and greater consistency. The plot reveals that AI models generally perform with higher accuracy and consistency compared to CBCT and MRI, while MRI shows the most concentrated, but lower, diagnostic accuracy.

Figure 5 illustrates the correlation between diagnostic metrics - accuracy, sensitivity, and specificity - across CBCT, MRI, and AI. CBCT *vs* AI (orange squares) demonstrates the strongest and most consistent correlation, indicating highly aligned diagnostic performance. MRI *vs* AI (grey triangles) shows moderately high but variable correlation, while CBCT *vs* MRI (blue diamonds) reflects the lowest correlation, suggesting limited agreement. Overall, the plot emphasizes AI's diagnostic reliability, closely mirroring CBCT, and outperforming MRI in consistency.

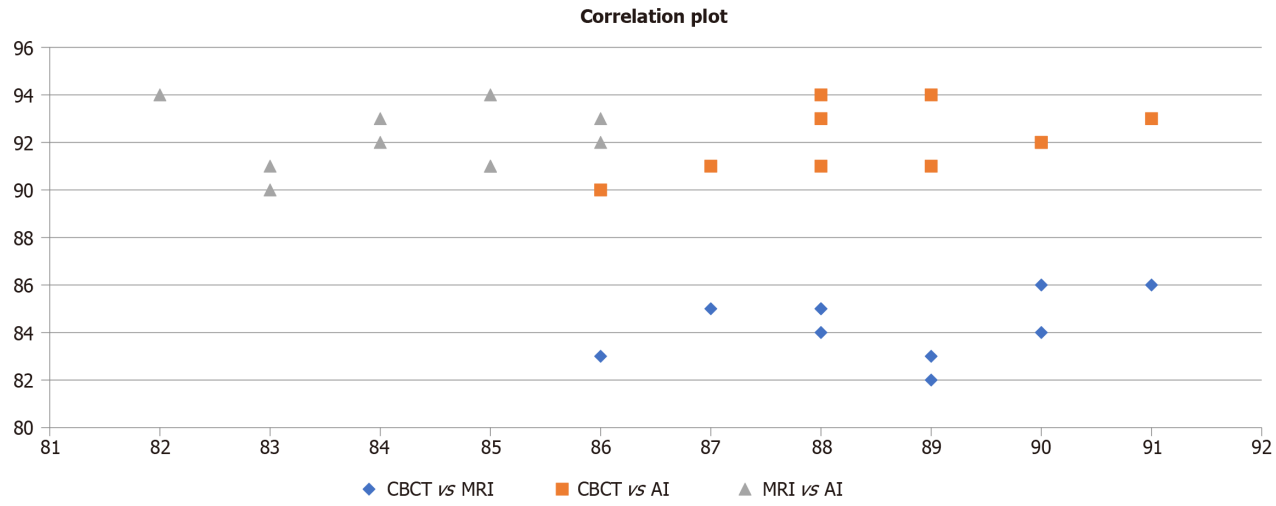


Figure 5 Correlation between diagnostic accuracy, sensitivity, and specificity across cone beam computed tomography, magnetic resonance imaging, and artificial intelligence modalities. CBCT: Cone beam computed tomography; MRI: Magnetic resonance imaging; AI: Artificial intelligence.

DISCUSSION

Introduction to periodontal-systemic interactions and AI in diagnostics

The integration of AI in healthcare, especially for diagnosing periodontal diseases, has significant potential in identifying systemic diseases such as T2DM, hypertensive cardiovascular disease, Alzheimer's disease, PCOS, thyroid disorders, DKD, and post-COVID complications. Previous research, such as Kovacic *et al*[20] in 2012, demonstrated that hyperglycemia accelerates periodontal disease progression, confirming the impact of systemic conditions on periodontal health. Zhukov *et al*[21] highlighted the exacerbating role of diabetes on periodontal disease progression, and this is consistent with the findings of Kovacic *et al*[20], who emphasized the bidirectional relationship between diabetes and periodontitis.

Effectiveness of AI models and diagnostic accuracy

The use of tailored AI models enhanced diagnostic accuracy and predictive capability. ML models excelled in structured data analysis and risk prediction, while DL models (especially CNNs) improved sensitivity and specificity in complex imaging analysis. NLP models processed large volumes of unstructured data, supporting faster diagnosis and better risk prediction. Integrating AI with clinical parameters like PPD, CAL, and BOP further refined diagnostic accuracy. ML models analyzed clinical markers and patient demographics for better risk stratification, DL models improved pattern recognition with imaging data, and NLP models extracted insights from clinical notes, enabling early detection and better disease progression prediction. Studies such as Torres-Dowdall *et al*[22] have shown that larger datasets and advanced AI techniques contribute to higher diagnostic accuracy. For instance, Torres-Dowdall *et al*[22] demonstrated the improvement in diagnostic accuracy when integrating clinical and radiographic data with AI, reflecting findings from studies that incorporate multi-omics data. Similarly, superior diagnostic accuracy when DL models were employed, supporting the effectiveness of advanced models in predicting periodontal-systemic interactions. The accuracy achieved by models integrating clinical parameters were PPD, CAL, and bone loss) aligns, which demonstrated the significant impact of clinical parameters on diagnostic performance.

AI's role in predicting disease progression and risk stratification

The integration of clinical parameters such as PPD and CAL has proven to be a robust predictor of disease progression in the diagnosis of periodontal diseases. This validates the work of Heitz-Mayfield[23] in 2024, who highlighted PPD and CAL as gold standards for periodontal assessment. Similar to Torres-Dowdall *et al*[22], AI models integrating these clinical markers were shown to provide superior predictive performance. The results emphasized BOP as a marker of disease progression, align with the clinical markers utilized in the AI model for early detection of disease. Moreover, the diagnostic utility of AI-driven models that incorporate clinical parameters like BOP and CAL is consistent with findings from Torres-Dowdall *et al*[22], showing that clinical features remain critical in identifying the severity of periodontal disease in patients with systemic conditions like diabetes and hypertension.

Advanced imaging and AI integration

Advanced imaging techniques like CBCT and MRI, when integrated with AI tools, improve diagnostic accuracy. Zhukov *et al*[21] demonstrated that CBCT contributed to 35% reduction in diagnostic errors, which was corroborated by studies that have reported significant benefits from using radiographic images in diagnostic processes. MRI and AI integration contribute to improved soft tissue diagnostics by 25%, highlighting MRI's role in soft tissue evaluation. AI's capacity to

improve diagnostic efficiency was clearly shown by its 40% reduction in diagnostic time. The integration of multi-omics data further strengthened predictive accuracy by providing a deeper understanding of disease progression at the molecular level. ML models identified patterns in genomic and proteomic data, while DL models combined multi-omics with imaging data to refine sensitivity and specificity. This multi-modal approach improved early diagnosis and clinical decision-making. This finding supports the broader consensus that AI models are highly effective in streamlining diagnostic workflows, significantly reducing diagnostic time, and improving clinical outcomes by making processes faster and more reliable.

Multi-omics integration and enhanced diagnostic performance

Multi-omics integration - combining genomic, proteomic, and metabolomic data - has been shown to improve the diagnostic performance of AI models. Studies by Torres-Dowdall *et al*[22] highlighted how the inclusion of multi-omics data enhances the model's ability to predict disease outcomes more accurately. Similar findings have shown that AI models integrating multimodal data offer more accurate and reliable predictions compared to models relying solely on single-modality inputs.

In our study, the inclusion of these multi-omics parameters significantly improved the predictive accuracy of AI models, aligning with the work of Torres-Dowdall *et al*[22] who emphasized the importance of multimodal integration for addressing complex diseases like periodontitis. This suggests that AI models with multi-omics data can better assess the complex and multifactorial nature of periodontal-systemic interactions.

The integration of AI in periodontal-systemic interaction diagnostics has continued to evolve with advances in model complexity and dataset sizes. The studies from Torres-Dowdall *et al*[22] and García-Romero-Pérez *et al*[11] align with our findings, showing how larger datasets, better integration of clinical and imaging data, and the application of advanced AI algorithms can improve diagnostic accuracy and predictive modeling. This growing body of evidence suggests that AI's role in diagnosing and managing periodontal-systemic interactions will only continue to expand with better model training and the inclusion of diverse data sources.

Limitations and challenges

While AI models have demonstrated significant improvements in diagnostic accuracy and predictive performance, certain limitations remain. Data bias, particularly from under represented patient groups, can lead to skewed predictions and reduced generalizability. Over fitting issues may arise when AI models are trained on limited or non-diverse datasets, reducing their performance on new data. Clinical implementation challenges include the need for large-scale, high-quality datasets, integration with existing clinical workflows, and ensuring regulatory compliance. Additionally, AI models require continuous retraining and validation to adapt to evolving clinical data and patient profiles. Addressing these limitations is essential for maximizing AI's potential in periodontal and systemic disease diagnosis.

CONCLUSION

This article underscores the transformative role of AI in the early diagnosis and risk prediction of periodontal-systemic interactions, particularly for chronic conditions such as T2DM, hypertension, and pancreatic cancer. AI models, especially those integrating clinical, radiographic, and multi-omics data, demonstrate superior diagnostic accuracy and predictive capabilities, significantly improving early detection and disease progression forecasting. AI-driven tools, including CBCT and MRI, enhance clinical efficiency and patient outcomes by reducing diagnostic time and maintaining high sensitivity and specificity. With ongoing advancements and larger sample sizes, the integration of multi-omics data into AI models enhances diagnostic accuracy and predictive performance, supporting early diagnosis and personalized treatment strategies. However, challenges such as data bias, overfitting, and clinical integration need to be addressed to fully realize AI's long-term potential and ensure consistent, reliable outcomes in diverse clinical settings.

FOOTNOTES

Author contributions: Das N contributed to the conceptualization, methodology, data collection, manuscript drafting and writing, and key revisions of the manuscript; Gade KR contributed to the literature review of the manuscript; Addanki PK contributed to the manuscript methodological support and manuscript review; Das N and Gade KR contributed to data analysis; Das N, Gade KR, and Addanki PK performed the final approval of the manuscript; and all authors thoroughly reviewed and endorsed the final manuscript.

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META-ANALYSIS

Association of neutrophil-lymphocyte ratio with cardiovascular and all-cause mortality in patients receiving chronic hemodialysis: Systematic review and meta-analysis

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Abstract

BACKGROUND

The neutrophil-lymphocyte ratio (NLR) has been proposed as a potential prognostic marker for mortality outcomes in various conditions, yet its association with chronic hemodialysis (HD) remains underexplored. We aim to study its utility by conducting a meta-analysis of this specific population.

AIM

To determine whether elevated NLR is associated with all-cause mortality (ACM) and cardiovascular mortality (CVM) in patients undergoing chronic HD.

METHODS

A comprehensive search from PubMed, Google Scholar, and Scopus identified studies showing the association between NLR and mortality outcomes in patients with chronic HD. Random-effects models with 95%CIs were employed to pool adjusted hazard ratios (aHRs), odds ratios (ORs), and I^2 statistics for evaluating the heterogeneity of findings. Leave-one-out sensitivity and meta-regression analyses assessed changes in overall effects and identified confounders, respectively. The Joanna Briggs Institute (JBI) tool was used to assess the quality of studies.

RESULTS

19 studies comprising 9047 patients with a mean age of 59.5 ± 5.86 years and a mean follow-up duration of 46.7 months were included in our study. Our meta-analysis revealed a significant association between NLR > 2.5 and increased risks of ACM (aHR: 1.25, 95%CI: 1.14-1.37, $P < 0.0001$) and CVM (aHR: 1.24, 95%CI: 1.02-1.49, $P = 0.03$). Studies reporting outcomes in OR reported similar findings for ACM (OR: 4.59, 95%CI: 1.74-12.11, $P = 0.002$) and CVM (OR: 1.11, 95%CI: 1.01-1.23, $P = 0.03$). Sensitivity analysis revealed no variations. Meta-regression revealed increasing male proportion is positively associated with ACM. Pooled area under the curve (AUC) was 0.71 (95%CI: 0.63-0.80, $P < 0.0001$). The JBI tool revealed high-quality studies.

CONCLUSION

This meta-analysis suggests that elevated NLR may serve as a useful prognostic marker for ACM and CVM in patients on chronic HD and can be useful in planning for the prevention of mortality-related strategies.

Key Words: Neutrophil-lymphocyte ratio; Chronic hemodialysis; Cardiovascular mortality; All-cause mortality; Inflammation; Inflammatory markers; Dialysis outcomes; Hematological biomarkers; Dialysis-associated cardiovascular disease

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Core Tip: This systematic review and meta-analysis evaluate the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in patients undergoing chronic hemodialysis (HD). Elevated NLR was significantly associated with increased all-cause and cardiovascular mortality in this population. By pooling adjusted hazard ratios and assessing heterogeneity and diagnostic performance *via* the area under the curve, the study highlights NLR as a potentially valuable and accessible biomarker for risk stratification in HD patients. Findings support its clinical use, while emphasizing the need for standardized cutoffs and prospective validation.

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by irreversible structural or functional abnormality and a decrease in the glomerular filtration rate (GFR) to less than 60 mL/minute per 1.73 m², along with or without biomarkers of renal damage lasting for more than or equal to three months[1]. The majority of them receive hemodialysis (HD). Still, it can progress to end-stage renal disease (ESRD) and necessitates renal replacement therapy, which includes HD, peritoneal dialysis (PD), and kidney transplantation[2]. Cardiovascular events and mortality are more likely to occur in these patients[2]. Based on data from the National Health and Nutrition Examination Survey from 2017 to March 2020, the United States Renal Data System's 2023 annual data report states that 14.0% of United States adults had an estimated GFR (eGFR) of less than 60 mL/minute/1.73 m², a urinary albumin-creatinine ratio (ACR) of at least 30 mg/g, or both. In the United States, the overall population's prevalence of CKD increased from 12.5% in 2009-2012 to 14% by March 2017-2020

[3]. Between 2001 and 2019, the incidence of ESRD rose by 37.8%; in 2020, it decreased by 3.1%, and in 2021, it sharply increased. In 2021, home HD was initiated for 0.4% of incident ESRD patients[3].

Many conventional inflammatory markers, including tumor necrosis factor-α, interleukin-6, and C-reactive protein, exacerbate kidney function impairment in patients with CKD[4]. CKD's hyperinflammatory state encourages atherogenesis and advances through vascular endothelial infiltration and leukocyte adhesion[5]. Cardiovascular etiology is the primary cause of mortality among patients with ESRD. Accelerated atherosclerosis leads to peripheral vascular disease, ischemic heart disease, and stroke. It is also associated with an enhanced risk of thrombotic events and venous thromboembolism, and can also lead to heart failure[6-8]. Patients undergoing dialysis have always had a higher adjusted mortality rate than other ESRD patients, and HD patients have a higher adjusted mortality rate than PD patients. Arrhythmia or sudden cardiac arrest is the leading cause of death among HD patients, accounting for 44%[3].

A computed composite inflammatory marker, the NLR, is based on the innate immune represented by the neutrophil count, and the adaptive immune and nutrition represented by the lymphocyte count[9]. The normal NLR values for adults, non-geriatric, and the population in good health are between 0.78 and 3.53 (mean: 1.65)[10]. However, racial differences have been studied in adult, non-institutional patients, in which it was found that non-Hispanic Black (1.76) and Hispanic (2.08) participants have significantly lower mean NLR values when compared to non-Hispanic whites (2.24), while the overall mean NLR was 2.15[11]. Previous meta-analyses have already proved that NLR is associated with an increased risk of all-cause mortality (ACM) and cardiovascular mortality (CVM) among patients with CKD[9]. In our study, we have studied whether NLR is associated with ACM and CVM among patients with ESRD undergoing chronic HD, with more updated data, performing subgroup, meta-regression, and pooled area under the receiver operating characteristic (ROC) curve (AUCROC) analysis for a thorough understanding of the association.

MATERIALS AND METHODS

We have conducted this study by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12].

Data sources and search strategy

We have used appropriate Medical Subject Headings (MeSH) terms, and a search was conducted in PubMed/MEDLINE, Google Scholar, and Scopus from 2013 to June 2024, which reported the association between the NLR and ACM or CVM among the patients receiving chronic HD. MeSH terms that we have utilized were "Hemodialysis," "dialysis," "Neutrophil-lymphocyte ratio," "Mortality," "survival," "prognosis," "Impact," "risk," "death," "Died," "cardiac arrest," and relevant articles and their full texts were collected for further assessment. A full list of search terms and an example search strategy for PubMed has been included in the Supplementary material. We have created a PRISMA chart that depicts the flow of inclusion and exclusion of articles with reasoning (Figure 1).

Inclusion and exclusion criteria

Articles retrieved from the search strategy were imported into Rayyan, and duplicates were removed; title and abstract screening was done by two independent reviewers, Roopeessh Vempati and Nanush Damarlapally, and any disparity was ruled out by a third reviewer, SV. In our study, we have included those observational studies, both prospective and retrospective, where the study population included adults with ESRD and undergoing chronic HD, NLR, and its association with outcomes, including ACM and CVM documented in the form of odds ratio (OR) or hazard ratio (HR) along with their 95%CI. We have excluded those studies where the study population is of pediatric age group, undergoing PD, animal studies, review articles, case reports, conference articles, editorials, animal studies, non-English articles, and those that reported no outcomes for the association of NLR with ACM or CVM in the form of ORs or HRs. In addition, we have excluded studies with incomplete data, which refer to studies that lacked sufficient information on NLR thresholds, mortality outcomes, or did not provide effect estimates such as OR or HR with 95%CI, making them unsuitable for inclusion in meta-analysis.

Data extraction and quality assessment

A Microsoft Excel sheet was utilized to extract the data points from the studies, including demographics, study characteristics, the predictive validity of the NLR on outcomes through AUC under the ROC curve, ORs, and HRs on the primary outcomes, that is, ACM or CVM was included in the study. Overlapping datasets were checked by comparing study authors, locations, and timeframes. In case of overlap, the most comprehensive or recent dataset was included. These studies were assessed for quality through the Joanna Briggs Institute (JBI) quality appraisal tool for cohort studies and are represented as traffic light and summary plot utilizing a generic template from Robvis software (Figure 2 and Supplementary Figure 1). Findings from the data extraction were represented in Tables 1 and 2 and Supplementary Table 1. The *P* values in Tables 1 and 2 reflect statistical comparisons between high and low NLR groups within individual studies, based on either unpaired *t*-tests or Mann-Whitney *U* tests, depending on data normality as reported by the original authors.

Statistical analysis

All statistical analysis was conducted with the help of Comprehensive Meta-analysis software version 4, by Biostat, Inc. In our study, we pooled the ORs and adjusted HR (aHR) by employing a random effects model with a 95%CI. Forest plots were utilized to visualize the pooled ORs and HRs in Figure 3. In addition, I^2 statistics were applied to look for hetero-

Table 1 Baseline characteristics of the study population from the included studies, *n* (%)/mean ± SD

Ref.	Type of study	Follow-up in years	Sample size	Age in years	Males	BMI (Kg/m²)	Serum albumin (g/dL)	Absolute neutrophil value (10^9/L)	Absolute lymphocytes value (10^9/L)	Total leukocytes (10^9/L)
Erdem *et al*[13]	P	1	59	55.6 ± 44	35 (59)	26.91 ± 6	3.85 ± 0.383	4.30 ± 1.57[a]	1.27 ± 0.35[a]	6.35 ± 1.6[a]
Abe *et al*[14]	P	N/A	86	57.6 ± 11.5	58 (67.4)	22.0 ± 4.0	3.5 ± 0.5	4.1 ± 1.7[a]	1.1 ± 0.4[a]	6.0 ± 2[a]
Neuen *et al*[15]	R	5	170	54 ± 11	102 (60)	26 ± 1.5	3.4 ± 0.13[a]	5.1 ± 1.7[a]	1.7 ± 0.57[a]	7.7 ± 0.59
Ouellet *et al*[16]	R	2	5782	62.5 ± 15.2[a]	3180(55)[a]	N/A	3.72 ± 0.48[a]	64.5 ± 10.7[a]	22.22 ± 9.01[a]	7.26 ± 2.56[a]
Yaprak *et al*[17]	P	N/A	80	56.8 ± 18.1	32 (40)	N/A	3.64 ± 0.47	3.904 ± 1.543	1.44 ± 0.5	N/A
Sato *et al*[18]	R	2	78	63.4 ± 11.7	51 (65.4)	23.4 ± 3.9	3.2 ± 0.5	N/A	N/A	6.3 ± 2.18[a]
Li *et al*[19]	P	N/A	268	48.7 ± 10.9	149 (55)	N/A	3.63 ± 0.35	N/A	N/A	N/A
Xiang *et al*[20]	P	6	355	58.0 ± 14.9[a]	220 (62)	21.5 ± 3.30	4 ± 0.9[a]	4.0 ± 0.3[a]	1.2 ± 0.09[a]	5.89 ± 0.39[a]
Woziwodzka *et al*[21]	P	5	84	61.5 ± 4.38	50 (59.5)	25.1 ± 1.21	4.2 ± 0.11[a]	N/A	N/A	6.9 ± 0.48[a]
Balboul *et al*[22]	R	N/A	554	67.6 ± 14.2	66 (12)	26.7 ± 6.0	3.47 ± 0.6	4.8 ± 0.52	1.3 ± 0.14	7.0 ± 0.59
Kular *et al*[23]	R	N/A	224	65.8 ± 14.4[a]	133 (59)	N/A	3.36 ± 6.32	4.67 ± 2.99[a]	0.903 ± 0.49	6.16 ± 3.18[a]
Oguz *et al*[24]	P	N/A	123	61 ± 15.6[a]	75 (61)	N/A	3.47 ± 0.65[a]	4.8 ± 3.1[a]	0.99 ± 0.89	6.6 ± 4.6[a]
Zhang *et al*[25]	P	5.9	360	60 ± 3.17	201 (56)	N/A	4.05 ± 0.08	4.05 ± 0.34[a]	1.17 ± 0.112[a]	N/A
Lano *et al*[6]	P	2	183	65.5 ± 16.3[a]	106(58)[a]	N/A	3.78 ± 0.56	4.3 ± 1.8[a]	1.29 ± 0.58[a]	6.9 ± 5.0[a]
Wang *et al*[26]	R	3	185	56.3 ± 13.8[a]	88 (47.6)	N/A	3.878 ± 0.36[a]	N/A	N/A	N/A
Parmelia *et al*[27]	P	1	186	56.3 ± 11.1	110 (59)	N/A	N/A	3.9 ± 0.38a	1.3 ± 0.12[a]	6.2 ± 0.38
Wang *et al*[28]	R	4.83	240	63.4 ± 13.7	161 (67)	N/A	3.754 ± 0.42[a]	N/A	N/A	N/A
Zhang *et al*[29]	R	7	303	53.7 ± 13.17	184 (61)	N/A	4 ± 0.23	4.1 ± 1.1	1.3 ± 0.3[a]	N/A
He *et al*[30]	P	N/A	168	55.4 ± 15.1[a]	101 (60)	N/A	4.15 ± 0.55	4.51 ± 1.84	1.38 ± 0.56[a]	N/A

[a]$P < 0.05$.

BMI: Body mass index; R: Retrospective; P: Prospective; N/A: Not applicable.

geneity in the outcomes of interest, ACM and CVM. Mild heterogeneity was considered for I^2 values between 25%-50%, moderate heterogeneity for the I^2 values between 50%-75%, and severe heterogeneity for the values greater than 75%. Furthermore, a leave-one-out sensitivity analysis was performed by removing each study and re-running the meta-analysis to calculate the effect size, CI, and *P* value each time to identify the influence of each study on the overall effect

Table 2 Baseline characteristics of the study population from the included studies

Ref.	Total Platelets (10^9/L)	NLR	Hb (g/dL)	S Ferritin (ng/mL)	S Creatinine (mg/dL)	Smoking	HTN	Stroke	DM	CRP (mg/dL)
Erdem *et al*[13]	222 ± 64	3.51 ± 0.95[a]	11.15 ± 0.9	N/A	9.75 ± 2.5	N/A	N/A	N/A	N/A	N/A
Abe *et al*[14]	206 ± 59	3.72 ± 4.9[a]	8.8 ± 1.3	148.9 ± 180.8	10.2 ± 3.4	16 (18.6)	N/A	21 (24.4)	N/A	N/A
Neuen *et al*[15]	N/A	3 ± 0.28[a]	10.8 ± 1.5[a]	483 ± 98	N/A	32 (19)	N/A	6 (3.5)	117 (69)[a]	N/A
Ouellet *et al*[16]	N/A	3.84 ± 3.27[a]	N/A	N/A	N/A	N/A	N/A	231 (4)	3007(52)[a]	N/A
Yaprak *et al*[17]	174 ± 56	2.52 ± 0.91	10.6 ± 1.5	1015 ± 513	7.68 ± 2.46	N/A	N/A	N/A	N/A	1.36 ± 2.00
Sato *et al*[18]	202 ± 92[a]	4.09 ± 6.94[a]	8.9 ± 1.3	82.6 ± 119.9	10.1 ± 3.2	N/A	77 (98.7)	7 (9.0)	N/A	0.24 ± 1.41[a]
Li *et al*[19]	N/A	3.36 ± 1.65	11.49 ± 1.27	N/A	10.33 ± 1.9	71 (26.5)	N/A	N/A	49 (18.3)	N/A
Xiang *et al*[20]	N/A	3.22 ± 0.3[a]	10.68 ± 1.52	0.15 ± 0.05[a]	11.46 ± 3.19	85 (23.9)	262 (74)	N/A	66 (18.6)	N/A
Woziwodzka *et al* [21]	N/A	3 ± 0.37	N/A	N/A	5 ± 0.43	20 (23.8)	71 (84.5)	3 (3.6)	25 (29.8)	7.4 ± 3.26
Balboul *et al*[22]	182 ± 16.4	3.55 ± 0.6	10.4 ± 1.5	N/A	6.42 ± 2.4	N/A	N/A	N/A	61	1.19 ± 0.65
Kular *et al*[23]	N/A	6.9 ± 8.4[a]	10.5 ± 1.5	N/A	N/A	71 (32)[a]	182 (81)	49 (22)[a]	120 (54)	N/A
Oguz *et al*[24]	174 ± 78	6.49 ± 7.88[a]	9.87 ± 1.65	1024 ± 1206[a]	N/A	49 (40)	93 (76)	N/A	53 (43)[a]	74 ± 96.82[a]
Zhang *et al*[25]	171.5 ± 15.3[a]	3.42 ± 0.4[a]	11.2 ± 0.35[a]	N/A	N/A	N/A	N/A	N/A	N/A	64 ± 30.63
Lano *et al*[6]	199 ± 83[a]	4.01 ± 2.6[a]	10.7 ± 1.2	562 ± 462	N/A	104 (57)	159 (87)	N/A	73 (40)	N/A
Wang *et al*[26]	N/A	3.365 ± 0.98[a]	10.99 ± 1.8	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Parmelia *et al*[27]	192.5 ± 12.27	3.2 ± 0.37[a]	10.3 ± 0.36	N/A	11.3 ± 3.3	N/A	146 (92)	N/A	31 (19.5)	N/A
Wang *et al*[28]	N/A	3.31 ± 1.36[a]	10.57 ± 1.85[a]	N/A	7.01 ± 2.86	N/A	N/A	N/A	N/A	N/A
Zhang *et al*[29]	172 ± 13.62[a]	3.22 ± 0.35[a]	10.6 ± 1.0	182 ± 71.64	11.3 ± 65.74	43 (14.19)	252 (83)	N/A	80 (26.4)	N/A
He *et al*[30]	198.03 ± 80.9[a]	3.63 ± 1.80[a]	10.4 ± 2.26	228.9 ± 350.9[a]	11.2 ± 3.8	N/A	23 (13.7)	N/A	44 (26.2)	N/A

[a]$P < 0.05$.

Hb: Hemoglobin; NLR: Neutrophil-lymphocyte ratio; S: Serum; HTN: Hypertension; DM: Diabetes mellitus; CRP: C-reactive protein; N/A: Not available.

size estimate (Supplementary Figure 2). We have also performed a subgroup analysis by dividing the data from the included studies into various categories and representing them in Table 3. On top of that, we have performed a meta-regression analysis to identify the confounding effect of other variables on ACM and CVM (Table 4 and Supplementary Figure 3). Pooled AUCROC analysis was performed to identify the discriminative or predictive ability and the diagnostic performance of NLR > 2.5 for the studied outcomes. An AUC value indicates the predictive performance of an

Table 3 Subgroup analysis of the included studies on the association of neutrophil-lymphocyte ratio with all-cause mortality

Variables	Number of studies	No. of patients	aHR (95%CI)	*P* value	I^2
Study design					
Prospective	5	786	1.63 (1.66-2.27)	0.004	67.1
Retrospective	6	7111	1.17 (1.07-1.29)	0.0008	87.7
Sample size					
≥ 200	5	7131	1.11 (1.02-1.21)	0.016	81.6
< 200	6	766	1.35 (1.16-1.56)	< 0.0001	52
Age (years)					
≥ 57	5	6722	1.07 (1.00-1.14)	0.048	72.2
< 57	6	1175	1.42 (1.21-1.67)	< 0.0001	57.4
Males%					
≥ 60%	4	719	1.30 (1.16-1.46)	< 0.0001	45.5
< 60%	7	7178	1.14 (1.03-1.25)	0.008	79.2
Diabetes (%)					
≥ 30	4	6730	1.14 (1.04-1.25)	0.008	91.2
< 30	5	1009	1.62 (1.20-2.19)	0.001	69.5
NLR					
≥ 3.5	5	6806	1.08 (1.02-1.14)	0.01	71.8
2.5-3.5	6	1091	1.54 (1.33-1.78)	< 0.0001	14
Hemoglobin (g/dL)					
≥ 10.5	5	1045	1.37 (1.06-1.76)	0.02	91
< 10.5	4	986	1.17 (1.00-1.36)	0.04	75.8
Creatinine (mg/dL)					
≥ 7.7	5	1003	1.42 (1.16-1.73)	0.0006	60.7
< 7.7	3	718	1.43 (0.77-2.67)	0.26	64
Serum albumin (g/dL)					
≥ 3.5	6	6685	1.53 (1.21-1.94)	0.0004	57.6
< 3.5	4	1026	1.13 (1.03-1.24)	0.007	90.6
Serum ferritin (ng/mL)					
≥ 340	3	418	1.29 (1.11-1.49)	0.0008	56.4
< 340	2	381	1.34 (1.09-1.64)	0.004	< 0.0001

NLR: Neutrophil-lymphocyte ratio; HR: Hazard ratio.

intervention, it can be 1.0 (perfect), 0.9-1.0 (excellent), 0.9-0.9 (very good), 0.7-0.8 (good), 0.6-0.7 (fair), 0.5-0.6 (poor), while 0.5 (random) or less indicates no or worse than random discrimination (Supplementary Figure 4). The publication bias was assessed using Egger's regression asymmetry test, and is represented as funnel plots. A *P*-value < 0.05 was considered indicative of small-study effects (Supplementary Figure 5).

Ethical considerations

As this study was done by pooling individual published studies for a systematic review and meta-analysis of previously published studies, no ethical approval was required.

Table 4 Meta-regression analysis of variables associated with all-cause mortality and cardiovascular mortality

Variables	Number of studies	Coefficient estimate	95%CI	*P* value
All-cause mortality				
Age	11	-0.02	-0.03 to 0.01	< 0.0001
Males	11	0.005	-0.003 to 0.01	0.22
BMI	4	-0.05	-0.23 to 0.12	0.55
Hypertension	6	0.002	-0.005 to 0.01	0.5
Diabetes	9	-0.005	-0.01 to 0.0006	0.08
CRP	4	0.1	-0.03 to 0.23	0.13
Hemoglobin	9	0.08	-0.08 to 0.24	0.32
Serum creatinine	6	0.06	-0.02 to 0.13	0.17
Serum ferritin	5	0.0004	-0.0001 to 0.0009	0.12
Serum albumin	10	0.17	-0.13 to 0.47	0.26
Smoking	5	-0.02	-0.06 to 0.02	0.28
Cardiovascular mortality				
Age	4	-0.02	-0.04 to 0.004	0.01
Males	4	0.005	0.003 to 0.008	< 0.0001
Diabetes	4	-0.004	-0.01 to 0.006	0.43
Hemoglobin	4	0.26	-0.04 to 0.56	0.09
Serum albumin	4	0.54	-0.75 to 1.83	0.41

BMI: Body mass index; CRP: C-reactive protein

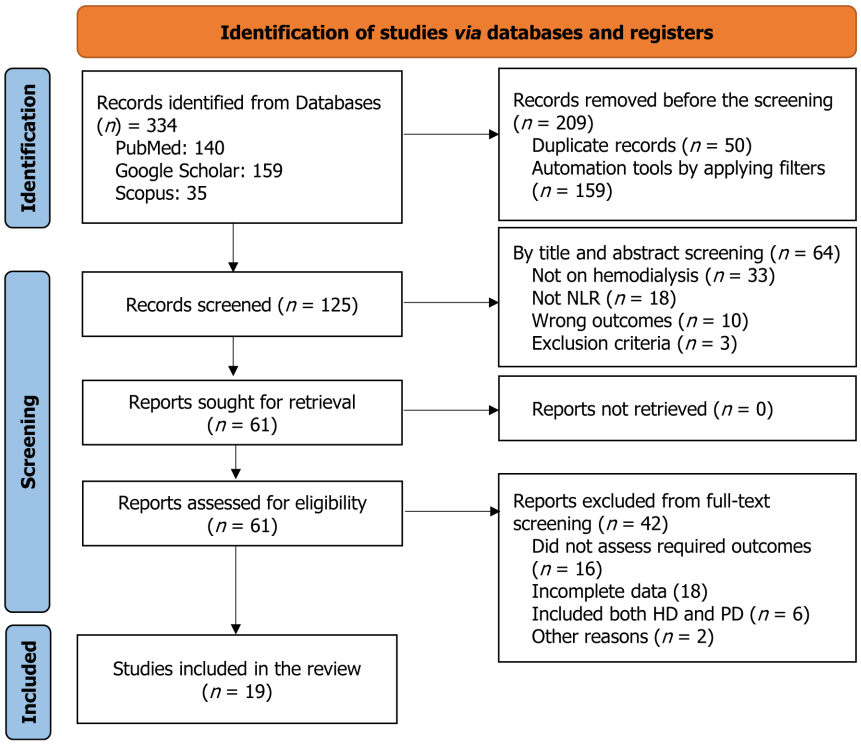


Figure 1 PRISMA flow chart. HD: Hemodialysis; PD: Peritoneal dialysis; NLR: Neutrophil-lymphocyte ratio.

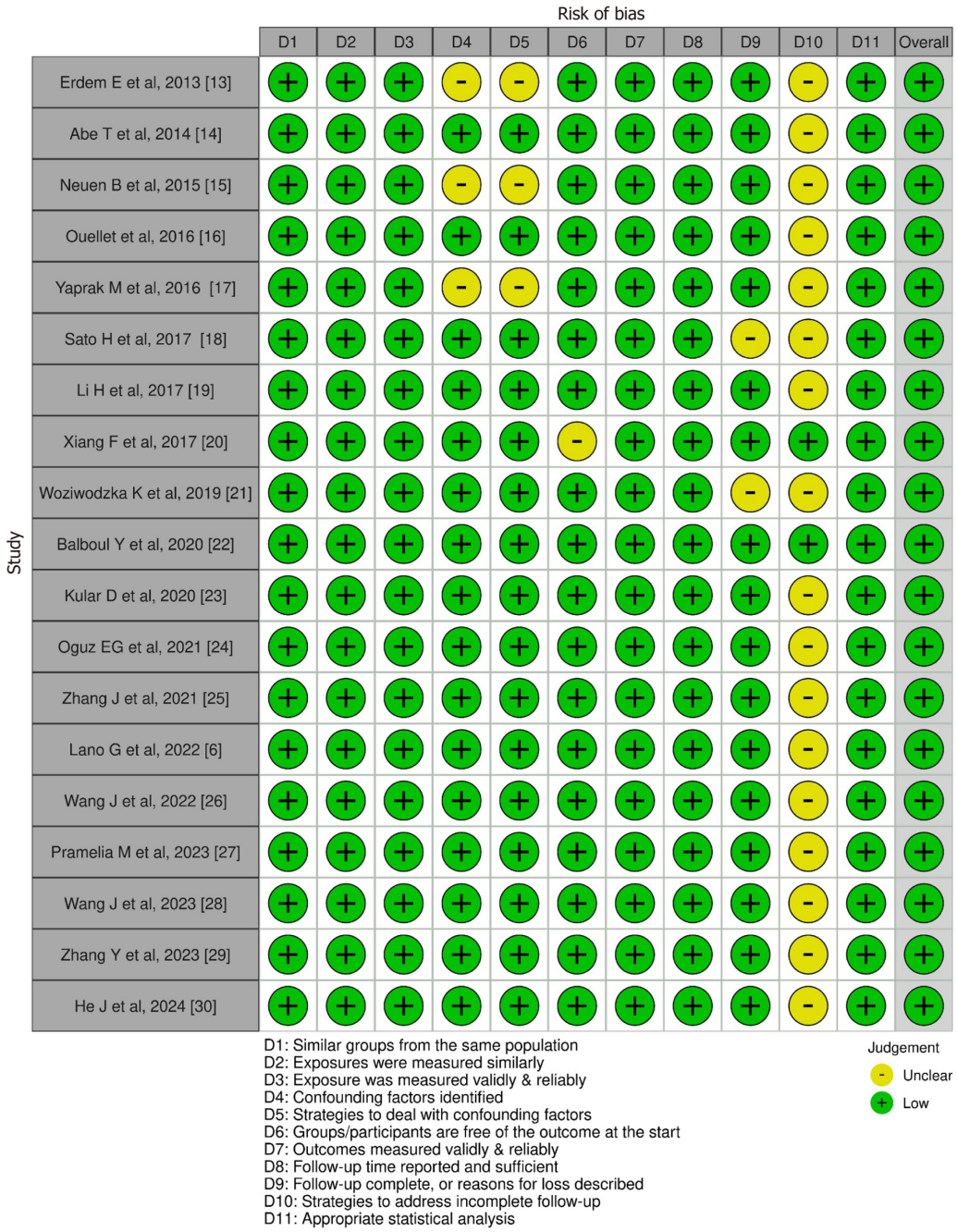


Figure 2 Risk of bias assessment was carried out using the Joanna Briggs Institute Tool and presented using Robvis software.

RESULTS

Literature search

A thorough search in Google Scholar, PubMed, and Scopus databases matching our selection criteria yielded 334 articles. Two independent reviewers (Roopeessh Vempati, Nanush Damarlapally), after removing 50 duplicates and 159 articles by applying filters through automation tools, screened the remaining 125 articles through their titles and abstracts, out of which 64 articles were removed which included those studies that were not on HD or NLR, those studied outcomes other than ACM and CVM, and those meeting the exclusion criteria. 61 articles were screened for full-text, out of which 42 articles were excluded. A third reviewer, Srivatsa Surya Vasudevan, resolved all the disparities. Finally, 19 studies[6,13-30] with a collective sample of 9047 patients were included in this meta-analysis. The PRISMA diagram shows the detailed selection process (Figure 1).

Baseline characteristics

The total sample size of the study population was 9047 individuals with a mean age of 59.5 ± 5.86 years and an average follow-up duration of 46.7 months. These studies included both prospective and retrospective designs. Several studies reported a high prevalence of comorbidities among the participants, including hypertension (ranging from 74% to 98.7%

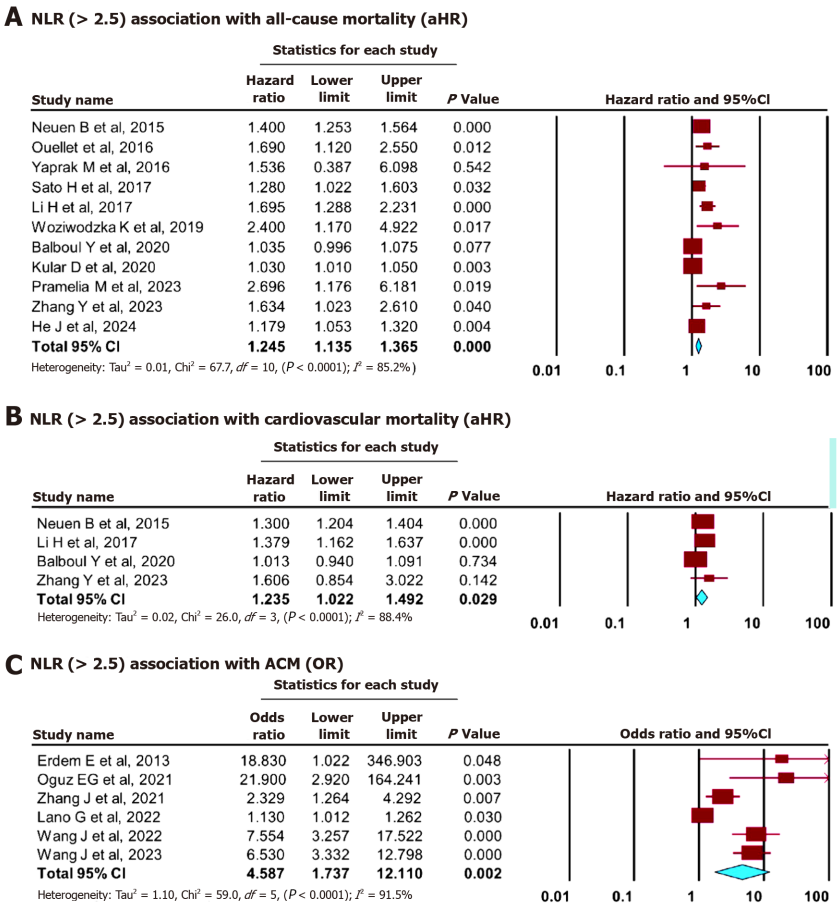


Figure 3 Forest plots illustrating the association. A: Neutrophil-lymphocyte ratio > 2.5 with all-cause mortality (hazard ratio); B: Cardiovascular mortality (hazard ratio); C: All-cause mortality (odds ratio). ACM: All-cause mortality; CVM: Cardiovascular mortality; OR: Odds ratio; HR: Hazard ratio.

in some studies), diabetes mellitus (up to 69%), and cerebrovascular diseases. The mean hemoglobin levels were generally around 10-11 g/dL, indicating the presence of anemia. Inflammatory markers such as CRP and ferritin were elevated, and serum albumin levels were low in many studies. Overall, these baseline characteristics highlight the diverse nature of the study populations and the significant burden of comorbidities in patients undergoing chronic HD. Further details about demographic and clinical characteristics of the population from the included studies, including age, sex distribution, dialysis therapy duration, and comorbid conditions like hypertension, diabetes mellitus, and cerebrovascular diseases, were reported in the baseline characteristics in Tables 1 and 2.

Quality assessment and publication bias

The JBI's quality appraisal tool for cohort studies was utilized and is represented as a traffic light plot by using the generic template in Robvis software[31,32] as in Figure 2, and a representation of a summary plot as in Supplementary Figure 1. The JBI tool questionnaire revealed high scores for almost all the studies, indicating a low risk of bias among the selected studies. Egger's regression asymmetry test showed significant publication bias in the association of NLR with ACM (P = 0.0007). However, no publication bias was found in the association of NLR with CVM (P = 0.60). The asymmetric shape of the funnel plot for the association of NLR with ACM and the symmetric shape for the association of NLR with CVM are both discernible in Supplementary Figure 5, which further demonstrates this point.

Clinical outcomes

In Supplementary Table 1, we have presented the various NLR cutoffs that were studied in the included studies, effect sizes of the outcomes, along with the various confounding variables that were adjusted for by the included studies. Figure 3 illustrates a forest plot showing the pooled HRs and ORs for ACM and CVM that conveys a significant association between a higher NLR (> 2.5) with an increased risk of both ACM and CVM in patients undergoing chronic HD. Most studies demonstrate a rightward shift from the null value of 1, which indicates that there is an increased risk of the outcomes studied associated with an elevated NLR. 95%CI not including 1 and P value < 0.05 indicates a statistically significant relationship.

ACM: The pooled analysis demonstrated that an NLR greater than 2.5 is significantly associated with an increased risk of ACM, with a pooled aHR (11 studies) of 1.25 (95%CI: 1.14-1.37; P < 0.0001; I^2 = 85.2%) and a pooled OR (4 studies) of 4.59 (95%CI: 1.74-12.11; P = 0.002; I^2 = 91.5%). The analysis revealed severe heterogeneity (I^2 > 75%) (Figure 3). In addition, subgroup analysis of the various variables associated with ACM revealed that most of the variables' categories

correspond to increased risk of ACM, including the NLR ranges of 2.5-3.5 and ≥ 3.5 (Table 3).

CVM: The association between NLR and CVM was similarly significant, with a pooled aHR (6 studies) of 1.24 (95%CI: 1.02-1.49; P = 0.03; I^2 = 88.4%). The pooled OR for CVM (2 studies) was 1.11 (95%CI: 1.01-1.23; P = 0.03; I^2 < 1%). The analysis for ACM displayed severe heterogeneity (I^2 > 75%) (Figure 3).

Sensitivity and meta-regression analysis

A leave-one-out sensitivity analysis, in which each study was sequentially excluded and the meta-analysis was repeated, demonstrated that no single study altered the overall effect size, confirming the robustness of the results (Supplementary Figure 2). Furthermore, to detect the presence of any confounding variables such as age, sex, or comorbid conditions, a meta-regression analysis was done. Meta-regression analysis showed that males proportion in the studies was positively associated with worsening CVM (coefficient: +0.005, 95%CI: 0.003-0.008, P < 0.0001) (Supplementary Figure 3). Additionally, increasing patients' age was inversely associated with both ACM (coefficient: -0.02, 95%CI: -0.03 to -0.01, P < 0.0001) and CVM (coefficient: -0.02, 95%CI: -0.04 to -0.004, P = 0.01), however strength of the co-efficient was very weak. Meta-regression of other variables for ACM or CVM did not show a statistically significant association, as presented in Table 4.

Pooled analysis of AUCROC

We have pooled the AUC values on the association of NLR and ACM to validate our findings and also to determine the discriminative or predictive ability of NLR for the studied association. Pooled AUC-ROC of 0.711 (95%CI: 0.63-0.80, P < 0.0001) indicates a good (AUC range: 0.7-0.8) discriminative ability of NLR > 2.5 in determining the risk of ACM in patients undergoing chronic HD (Supplementary Figure 4). Pooled AUC-ROC analysis for CVM was not feasible as only very few studies reported the values.

DISCUSSION

Principal findings

Our study demonstrates that elevated NLR > 2.5 is significantly associated with both ACM (aHR = 1.25, OR = 4.59) and CVM (aHR = 1.24, OR = 1.11) in patients undergoing chronic HD (Figure 3). These findings underscore the potential of NLR as a non-invasive, cost-effective prognostic biomarker in a high-risk ESRD population. Our findings align with and expand upon the previous meta-analysis by Ao *et al*[9], which reported a significant association between elevated NLR and risk of mortality in patients with CKD. However, Ao *et al*[9] focused on patients at various stages of CKD, whereas our analysis was exclusive to patients with ESRD receiving chronic HD.

Pathophysiological rationale

CKD results in a sustained systemic inflammatory response that impacts vascular and myocardial structures. This inflammation facilitates the development of atherosclerotic plaques in the vessels, contributes to vascular calcification and senescence, and leads to myocardial fibrosis as well as calcification of heart valves[33]. When a systemic inflammatory immune response brought on by tissue damage results in a decrease in the number of lymphocytes and the suppression of neutrophil apoptosis and neutrophil-mediated killing as part of the innate immune response, the NLR can rise[34]. The immune system's natural physiological response to supraphysiologic insults controlled by the nervous system, including the sympathetic and parasympathetic systems as well as the endocrine system, is a change from the adaptive to the innate immune system[35]. This is caused by stress hormones like catecholamines, cortisol, and prolactin, causing neutrophilia and lymphocytopenia, respectively, by demarginating the lymphocytes and marginating the neutrophils[35]. Neutrophils play a pivotal role in the innate immune system, including phagocytosis, release of cytokines, and inflammatory mediators[35]. High NLR was found to be an independent predictor of long-term death from coronary heart disease[36]. The pathophysiology of atherosclerosis and endothelial dysfunction is specifically influenced by inflammation and oxidative stress, which are typified by the activation of the NLRP3 inflammasome[36].

Clinical implications of NLR in CKD and ESRD

The non-microbial inflammatory state indicated by neutrophils, and the overall stress and nutritional status, which is indicated by lymphocytes, causes the progression of CKD[37]. In a way, NLR generally reflects the degree of inflammation in CKD patients[37]. Tumor necrosis factor-a, C-reactive protein, and interleukin-6 are among the inflammatory markers that are elevated in patients with ESRD[38]. Furthermore, NLR can indicate the progression of stage IV CKD to the dialysis stage[39]. The conventional CKD risk factors, such as ACR and eGFR, have no bearing on this correlation of progression among CKD patients[37]. When GFR declines, CKD progresses to ESRD, and the risk of cardiovascular disease and death increases[40]. Among ESRD patients receiving HD, we found a significant correlation between NLR, a measure of inflammatory status, with ACM and CVM.

Dialysis modality and comparative mortality

HD, PD, or continuous renal replacement therapy are options for patients with CKD[41]. Whether patients receiving HD have a higher mortality rate than those receiving PD is not clear[41,42]. In a recent meta-analysis by Chander *et al*[41], PD was associated with lower mortality risk than HD, but the significance was lost in the sensitivity analysis. A large

retrospective study of 449652 patients using the United States renal data system and Medicare found similar mortality for HD and PD[42].

NLR across various diseases

In addition to atherosclerosis[43], NLR was also studied in various pathologies including myocardial infarction[44], acute stroke[45], bacterial or fungal infection[34], severe trauma[46], cancer[47], complications from post-op surgery[48], type 2 diabetes[49], pulmonary arterial hypertension[50], obstructive sleep apnea syndrome[51], chronic obstructive pulmonary disease[52], spontaneous intracerebral hemorrhage[53], peripheral arterial occlusive disease[54], sepsis[55], and coronavirus disease 2019[56].

Comparison with other biomarkers

Studies had reported various similar biomarkers, and their independent predictability was debated. In a study by Yaprak *et al*[17], platelet lymphocyte ratio (PLR) but not NLR, Xiang *et al*[20] found monocyte lymphocyte ratio (MLR), but not NLR, was found to predict ACM independently. In addition, Zhang *et al*[29] found that high PLR predicts both ACM and CVM, while high NLR could predict only ACM. On the other hand, Chen *et al*[57] found that NLR, but not CRP or PLR, is an important prognostic predictor of all major clinical outcomes in patients with advanced CKD. In addition to NLR, serum ferritin could also predict the ACM among patients undergoing HD.

Insights from meta-regression analysis

Meta-regression analysis revealed increasing male proportion across the studies was positively associated with cardiovascular mortality, which is in line with the current evidence[58,59]. CKD/ESRD was found to be associated with disruption of sex hormone physiology[59]. A decrease in testosterone due to CKD or ESRD is found to be associated with CVM, but no association between a decrease in estradiol level to CVM was found in females[59]. On the other hand, in our meta-regression analysis, we found a weak inverse yet a debatable relationship between increasing age and ACM or CVM, which raised concerns that NLR may be a less useful predictor of mortality in the older population. Furthermore, with increasing age, there exists a state of chronic, low-grade inflammation, raising baseline inflammatory markers, including NLR, which may diminish their discriminative ability or effectiveness in risk assessment[60,61].

Limitations

Severe heterogeneity was found in the pooled estimates (> 75%) (Figure 3). It's important to acknowledge this as a limitation, and it can be due to various factors inherent in the included studies, as they were observational by study design, and are susceptible to certain biases, such as selection bias and confounding. There was also variability in the definition of NLR (Supplementary Table 1), the patient populations, and the endpoints reported, which might have contributed to heterogeneity. Despite having a large number of patients included in our study, the population of each study may not represent the real-world population. On top of that, the included studies varied considerably in sample size, ranging from 59 to 5782 participants. Studies with larger sample sizes provide more precise estimates of the association between NLR and mortality. Differences in sample size, along with variations in study populations and methodologies, and NLR thresholds, likely contributed to the severe heterogeneity (I^2 > 75%) (Figure 3). Additionally, the effect size may vary depending on various factors like comorbidities and dialysis duration. While most studies scored well on the JBI assessment, some had limitations in terms of clearly reporting follow-up procedures or addressing potential confounders, which could introduce some degree of bias (Figure 2). Egger's regression test revealed significant publication bias in studies examining the relationship between the NLR and ACM (P = 0.0007). This indicates that smaller or non-significant studies may be underrepresented, which could inflate the pooled effect estimate. The funnel plot for ACM displayed clear asymmetry, reinforcing this concern. In contrast, no publication bias was found for cardiovascular mortality (P = 0.60). These findings emphasize the need for cautious interpretation of the results related to ACM and highlight the importance of balanced publication practices (Supplementary Figure 5). Nevertheless, we reported sensitivity, subgroup, meta-regression analyses, and pooled AUC-ROC analysis, making our study reliable (Table 3, Supplementary Figures 2-4). Additionally, we were unable to study the potential confounding effect of infections, medication effects (*e.g.*, anti-inflammatory agents or phosphate binders), and dialysis adequacy (*e.g.*, Kt/V) on the studied outcomes as they were inconsistently or not uniformly reported in the included studies, limiting our ability to perform a subgroup or meta-regression analysis with these potential confounders.

Strengths

Nevertheless, our study had various strengths, including the large sample size, and analysis based on aHRs allowed us to account for potential confounding variables. Many studies had a prospective design (11/19), which strengthens the ability to assess the association between NLR and future mortality outcomes (Table 1). Our assessment using the JBI's quality appraisal tool revealed higher scores, as indicated through the traffic light plot that the included studies had a low risk of bias (Figure 2 and Supplementary Figure 1). In addition, we have identified no variations in the leave-one-out sensitivity analysis, where no single study disproportionately influenced the overall effect size for either ACM or CVM, and the association between NLR and mortality outcomes remained consistent across various study designs and populations, conveying the robustness of our study findings (Supplementary Figure 2). It implies that the significance of the association between NLR and mortality was not dependent on any individual study. While no single study altered the significance of our results, studies with larger sample sizes, such as Ouellet *et al*[16], naturally had a greater influence on the pooled estimates.

NLR is an easily available and cost-effective index for clinical practice, which makes it an attractive prognostic index for patients with CKD[9]. The pooled area under ROC curve analysis indicated that NLR could correctly classify the ACM in 71.1% ($P < 0.0001$) of the cases, and also indicates moderate effectiveness as a predictive biomarker (Supplementary Figure 4).

Furthermore, we performed a meta-regression analysis to study the influence of various confounders on the ACM and CVM in patients undergoing HD (Supplementary Figure 3), and we also assessed the publication bias using Egger's test, represented by funnel plots enhancing the reliability of our study (Supplementary Figure 5) which indicates the credibility of our meta-analysis.

Future directives

Future studies should investigate finding the most appropriate NLR threshold for a specific HD population by considering age, sex, and other comorbidities, as NLR is a non-specific marker. Large, multicenter prospective studies with a standardized population and subpopulation analysis are needed to generalize the findings. In addition, interventional studies should investigate the modifications in dialysis, like increased dose, altered composition, and the role of anti-inflammatory agents, nutritional interventions, and lifestyle modifications, to see if there is a reduction in the high mortality burden in this population.

CONCLUSION

This meta-analysis suggests that an elevated NLR is associated with an increased risk of all-cause and cardiovascular mortality among patients undergoing chronic HD. The pooled aHR and area under the curve analyses support the potential of NLR as a readily available and cost-effective prognostic biomarker. However, due to heterogeneity in study designs and thresholds used, these findings should be interpreted with caution. Future prospective studies with standardized methodologies are warranted to better establish the clinical utility of NLR in this high-risk population.

FOOTNOTES

Author contributions: Desai R conceptualized and designed the study, developed the methodology and software, performed formal analysis, provided resources, participated in writing and editing the manuscript, and managed project administration; Surani S and Ratnani I conducted formal analysis, provided resources, reviewed and edited the manuscript, and managed project administration; Vempati R and Patel V contributed to methodology, performed screening and feasibility assessments, conducted data curation and data extraction, drafted the original manuscript, reviewed and edited the manuscript, and supervised the project; Damarlapally N participated in screening and feasibility assessments, performed data extraction, and contributed to writing the original draft and reviewing and editing the manuscript; Vasudevan SS performed statistical analysis and contributed to writing the original draft and reviewing and editing the manuscript; Banda P contributed to data extraction, writing the original draft, and reviewing and editing the manuscript; Mourad D and Polamarasetty H participated in data extraction and manuscript review and editing; Mathur G and Khan A contributed to data extraction; All authors have read and approved the final manuscript.

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CASE REPORT

Need for combined therapy for a rare case of autoimmune autonomic ganglionopathy: A case report

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Abstract

BACKGROUND

Autoimmune autonomic ganglionopathy (AAG), formerly known as acute pandysautonomia, is a rare, acquired, antibody-mediated, potentially curable autonomic disorder that presents with diffuse autonomic failure. High levels of anti-ganglionic nicotinic acetylcholine receptor (gAChR) serum antibodies are detected in approximately 50% of AAG cases, confirming the diagnosis.

CASE SUMMARY

We present the case of a 68-year-old man who developed autonomic failure gradually over a 2-year period. Recently, the patient was unable to stand upright for more than a few seconds before fainting. Additionally, he presented with decreased sweating, dry mouth, urinary retention, early satiety, weight loss, bloating, constipation, and erectile dysfunction. Neurological examination revealed dilated pupils that were unresponsive to light. Deep tendon reflexes were absent or diminished. Serologic evaluation revealed the presence of gAChR autoantibodies. An orthostatic hypotension test yielded a positive result. The patient did not respond to symptomatic therapy, including midodrine, fludrocortisone and atomoxetine. Second-line therapy with immunoadsorption produced a noticeable clinical improvement; however, orthostatic hypotension persisted. Sequential rituximab infusion therapy successfully led to a significant improvement in symptoms.

CONCLUSION
Our case report supports the benefit of combined immunomodulatory therapy for refractory AAG cases that are unresponsive to single-agent treatment.

Key Words: Autoimmune autonomic ganglionopathy; Immunoadsorption; Combined immunomodulatory therapy; Refractory autoimmune symptoms; Rituximab; Case report

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Core Tip: This case highlights the potential benefit of combined immunoadsorption and rituximab therapy in refractory autoimmune autonomic ganglionopathy. Despite first-line therapy failure, the patient achieved significant long-term improvement, suggesting that a stepwise immunomodulatory approach may be necessary in resistant cases.

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INTRODUCTION

Autoimmune autonomic ganglionopathy (AAG) is a rare disorder characterized by autonomic failure, first described by Young *et al*[1] in 1969. It is defined by the presence of ganglionic nicotinic acetylcholine receptor (gAChR) antibodies, which are implicated in approximately half of all cases[2]. These receptors, composed of two α3 and three β4 subunits, mediate fast synaptic transmission across the sympathetic, parasympathetic, and enteric autonomic ganglia, with AAG-associated antibodies specifically targeting the α3 subunit[2]. The severity of autonomic dysfunction correlates with serum gAChR antibody titers; however, these titers do not reliably predict whether the disease will manifest acutely, subacutely, or chronically[3]**.** The pathological mechanisms involve functional receptor blockade, receptor internalization, and complement-mediated neuronal damage, leading to severe dysautonomia[3]. In some cases, T-cell-mediated autoimmunity and neuronal inflammation may also contribute to disease progression[3].

Clinically, AAG is characterized by widespread autonomic failure, affecting multiple organ systems. Patients typically present with severe orthostatic hypotension, recurrent syncope, anhidrosis, sicca syndrome (xerostomia and reduced lacrimation), neurogenic bladder, and gastrointestinal dysmotility, including gastroparesis and severe constipation[4]. Additionally, pupillary abnormalities, such as tonic or poorly reactive pupils, are commonly observed[4]. The disease predominantly affects middle-aged individuals (mean age 45-61 years), with a female predominance[4]. While idiopathic in most cases, AAG can also arise as a paraneoplastic syndrome or in association with autoimmune conditions such as Sjögren's syndrome or systemic lupus erythematosus[5].

We present a case of AAG with severe autonomic dysfunction, including profound orthostatic hypotension, neurogenic bladder, and gastrointestinal dysmotility, that was refractory to standard symptomatic first-line therapies. Despite limited improvement with immunoadsorption alone, the patient exhibited substantial clinical recovery following the introduction of rituximab alongside pyridostigmine. This case highlights the potential role of combined immunotherapy in refractory AAG and suggests a possible advantage of immunoadsorption over plasma exchange (PE) in select cases.

CASE PRESENTATION

Chief complaints

A 68-year old man presented to the Emergency Department of Internal Medicine, Hippokration University Hospital (Thessaloniki, Greece), with a 2-year history of progressively worsening orthostatic syncope. Recently, he was unable to stand upright for more than a few seconds before experiencing a syncopal episode. He also reported autonomic dysfunction symptoms, including decreased sweating, sicca syndrome, urinary retention, erectile dysfunction, early satiety, abdominal distention, and severe constipation that resulted in weight loss.

History of present illness

The patient reported a 2-year history of progressively worsening orthostatic syncope.

History of past illness

No preceding acute illness, including diabetes mellitus, Guillain Barré, or amyloidosis, nor identifiable cause had been found in a previous workup.

Personal and family history

The patient had no significant past medical history. He was an active smoker. His father had a history of arterial hypertension, and his mother had diabetes mellitus.

Physical examination

On physical examination, he weighed 60 kg (with a body-mass index, defined as the weight in kilograms divided by the square of the height in meters, of 19.6) and had warm, dry skin. His supine blood pressure was 150/70 mmHg, with a marked postural drop to 80/40 mmHg upon standing, without compensatory tachycardia. He experienced syncope within one minute of standing. His pupils were dilated and unresponsive to light. Deep tendon reflexes were absent or diminished in both upper and lower extremities, though muscle strength and sensation remained intact. The abdomen was distended with sparse bowel sounds and tympanitic percussion. Nerve conduction studies were normal.

Laboratory examinations

Serum samples for antibody detection were collected before treatment. Antibodies binding to neuronal gAChR were detected using a radioimmunoprecipitation assay (RIA)[6]. This assay utilizes a solubilized acetylcholine receptor (AChR) from a human neuroblastoma cell line (IMR-32) that is labeled with a high-affinity radioligand, ^{125}I-labeled epibatidine[7] and was performed by the Institute Pasteur Hellenique, Athens, Greece. The threshold for a definite positive result for gAChR antibodies targeting α3 subunit was set at 15 pmol per liter (pmol/L). Our patient's antibody level was 235 pmol/L.

Testing for myasthenia gravis, including measurement of muscle AChR antibodies, antibodies to membrane-linked muscle-specific kinase (MuSK) and antibodies to lipoprotein receptor-related protein 4 (LRP4), was negative (Table 1). Comprehensive diagnostic anti-neuronal antibodies panels were also negative (Table 2).

Imaging examinations

Abdominal computed tomography scan revealed thickening of the right colon at the ileocolic junction and in the ascending colon and a suspected renal pelvis tumor (likely originating from transitional epithelium). The biopsy was inconclusive and a pigtail catheter was placed. However, repeated urinary cytology showed no evidence of malignant cells. Moreover, a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan showed no metabolic activity suggestive of malignancy.

First-line therapy, including volume expansion (normal saline and fludrocortisone), vasoconstrictors (midodrine and atomoxetine), and nonpharmacologic measures (such as compression stockings), were ineffective. Given the persistent orthostatic intolerance and refractory symptoms, sequential therapy with pyridostigmine, immunoadsorption (second-line therapy), and rituximab (third-line therapy) was initiated, leading to symptomatic improvement, as described below.

FINAL DIAGNOSIS

The patient presented with progressive autonomic dysfunction, prompting an extensive differential diagnosis. Primary and secondary causes of autonomic dysfunction were systematically excluded, including neurodegenerative disorders (*e.g.*, multiple system atrophy), metabolic and endocrine abnormalities (*e.g.*, diabetic autonomic neuropathy and adrenal insufficiency), infectious and paraneoplastic syndromes, and medication-induced autonomic impairment. The presence of high-titer anti-gAChR antibodies strongly supports an immune-mediated pathogenesis. The exclusion of alternative causes and the presence of these disease-specific autoantibodies confirmed AAG as the most likely etiology of the patient's autonomic failure.

TREATMENT

The patient exhibited no response to first-line therapy, which included volume expansion, vasoconstrictors (midodrine and atomoxetine), and nonpharmacologic strategies. Severe orthostatic dizziness and syncope persisted, significantly impairing his mobility. Notably, he experienced several head trauma episodes due to falls when attempting to stand and walk unassisted, despite medical advice to remain supine. Given the refractory nature of his symptoms and limited literature on the optimal management of AAG, we chose immunoadsorption as a second-line therapy[7]. The patient underwent nine cycles of immunoadsorption, after which he exhibited neurological improvement. Specifically: (1) Cranial nerve function: Hoarseness improved, and lacrimal gland function showed partial recovery, leading to decreased ocular dryness; (2) Deep tendon reflexes: Previously absent lower limb reflexes became detectable, suggesting improved ganglionic synaptic transmission; (3) Autonomic function: He reported improvement in constipation, indicating partial recovery of enteric nervous system activity; and (4) Orthostatic tolerance: The patient was able to stand and walk without severe dizziness, though orthostatic hypotension remained abnormal on testing.

Table 1 Autoantibody control for myasthenia gravis

Exam	Method	Result	Result classification		
			Negative	Grey-zone	Positive
Anti-AChR	RIA	< 0.1 nmol/L	≤ 0.1	0.2-0.5	≥ 0.6
Anti-MuSK	RIA	< 0.015 nmol/L	< 0.015 nmol/L	0.015-0.03	> 0.03
Anti-LRP4	IFA (cell based assay)		< 10	10	> 10

Anti-AChR: Acetyl-Choline receptor ganglionic neuronal auto-antibodies; Anti-MuSK: Muscle-specific tyrosine kinase auto-antibodies; Anti-LRP4: Low-density lipoprotein receptor-related protein autoantibodies; RIA: Radioimmunoprecipitation assay, IFA: Indirect immunofluorescence assay.

Table 2 Antineuronal antibodies control

Exam	Method	Result	Result classification		
			Negative	Grey-zone	Positive
NMDA-R	IFA (cell based assay)	< 10	< 10	10	> 10
AMPA-R1		< 10			
GABAB-R		< 10			
LGI1		< 10			
DPPX		< 10			
CASPR2		< 10	< 10	10	≥ 100

NMDA-R: N-Methyl D-aspartate Receptor; AMPA-R1: A-amino-3-hydroxy-5-Methyl-4-isoxazolepropionic acid Receptor; GABAB-R: Gamma-amino butyric acid B Receptor; LGI1: Leukin-rich glioma inactivated; DPPX: Dipeptidyl-peptidase-like protein 6; CASPR2: Contactin-associated protein-like 2.

OUTCOME AND FOLLOW-UP

One month after immunoadsorption, a reassessment was performed, and given the incomplete symptomatic response, we initiated four cycles of intravenous rituximab as third-line therapy, while continuing pyridostigmine. During a 12-month follow-up, his symptoms markedly improved: He remained syncope-free, constipation resolved, and lacrimation and salivation normalized. Most notably, orthostatic hypotension testing was normal, indicating substantial autonomic recovery.

DISCUSSION

The traditional second-line approach to AAG treatment includes PE, which functions by removing pathogenic antibodies and other inflammatory plasma components. However, PE is associated with several complications, including thrombosis, bleeding, hypotension, sepsis, and allergic reactions[8]. More recently, immunoadsorption has been recognized as a promising alternative to PE, with the advantage of selectively removing immunoglobulins while preserving other plasma components, thereby reducing the need for volume replacement solutions[9]. In our case, we opted for immunoadsorption over PE, given its favorable safety profile and theoretical advantages in selectively reducing pathogenic autoantibodies, and we observed neurological improvement following nine treatment cycles. Another second-line treatment choice, widely used in immune-mediated neuropathies, is intravenous immunoglobin, though its efficacy in AAG remains variable[7].

When either PE, immunoadsorption, or intravenous immunoglobulin is used as a single therapy, subsequent treatments are required in most relapsing patients to maintain the improvement[7]. Other immunosuppressants, including azathioprine, cyclophosphamide, and mycophenolate mofetil, have been used in some cases, but their success is inconsistent[5]. In our patient, first-line symptomatic therapies failed to provide any benefit, leading us to escalate to second-line therapy with immunoadsorption, which resulted in partial neurological recovery but persistent orthostatic hypotension. As a result, the addition of other immunomodulatory therapies, particularly B-cell depleting agents, has emerged as a rational treatment strategy. Limited data exist on the efficacy of combination therapy in AAG, and only a few cases have reported the use of rituximab or immunoadsorption in seropositive AAG[3,5,7,10,11].

Rituximab, a monoclonal antibody targeting the CD20 antigen on B cells, has been successfully used in autoimmune neurological diseases, including AAG, but its use remains off-label and is based on case reports[8]. Rituximab is thought to deplete B cells, reduce disease-specific antibody production, and exert immunomodulatory effects on T cell signaling

[8]. Some reports indicate that rituximab may induce clinical remission even in cases where antibody titers remain elevated, suggesting that pathogenic mechanisms beyond gAChR autoantibodies-such as postganglionic sympathetic dysfunction-may contribute to AAG[12,13]. In our case, the addition of rituximab as third-line therapy resulted in marked improvement in orthostatic tolerance, resolution of syncope, and recovery of autonomic functions, an effect that persisted during 12 months of follow-up.

In our case we evaluated the patient based solely on clinical improvement and not on serological control. According to existing data, serum antibody levels are not always correlated with the clinical course with some cases indicating discordance between clinical severity and antibody titers[4]. The results by Gibbons and colleagues[3] were consistent with prior reports that reveal no relationship between the temporal profile (acute, subacute, or chronic) and antibody titers, symptom complex, response to therapy or clinical course. The patient described by Iodice *et al*[7] had significantly elevated antibody titers after intravenous immunoglobulin therapy. In an earlier report, rapid clinical improvement of AAG with rituximab occurred without a significant decline in gAChR antibody level[12]. This discrepancy may imply that perhaps other pathogenic mechanisms besides gAChR antibodies exist, such as the dysfunction of postganglionic sympathetic pathways[14]. Quantitative testing with validated autonomic biomarkers has been recently proposed to guide clinical management and monitor treatment response in patients with AAG[15]. Our case provides valuable insights into the treatment approach for refractory AAG. Specifically, combination therapy with immunoadsorption and rituximab may be an effective option in patients resistant to first-line symptomatic therapy. Immunoadsorption may serve as a safer and more targeted alternative to PE, including other autoimmune neurological disorders. The long-term benefit of rituximab in our patient highlights the potential for sustained remission with B-cell depletion therapy, warranting further investigation into its role as a second- or third-line treatment.

Although promising, the use of rituximab in AAG remains limited by several factors, including high cost, potential immune escape leading to reduced efficacy over time, and the risk of severe complications such as progressive multifocal leukoencephalopathy[9,10]. Further prospective studies are required to establish optimal treatment strategies, determine the most effective combination of immunotherapies, and evaluate the long-term safety and efficacy of rituximab in AAG and related autonomic disorders.

CONCLUSION

In conclusion, we present a patient with AAG of Greek origin who demonstrated resistance to initial first-line symptomatic therapy. Second-line therapy with immunoadsorption was not enough alone to control symptoms adequately and therefore third-line therapy with rituximab was added. This case presentation adds to the understanding of combined therapy in AAG and highlights a possible benefit of the implementation of immunoadsorption instead of PE. Further studies are essential to clarify the ideal treatment options for AAG.

FOOTNOTES

Author contributions: Angeloudi E, Xanthopoulou M, Liakos A, and Gigi E conceptualized the study; Angeloudi E, Xanthopoulou M, Liakos A, and Gigi E developed the methodology; Ioannidis P, Lima M, and Gigi E validated the findings; Angeloudi E, Xanthopoulou M, Liakos A, Gigi E, Kalyvas AC, and Ioannidis P conducted the investigation; Kalyvas AC, Dimitriou M, and Kotoulas SC provided resources; Angeloudi E, Xanthopoulou M, Kalyvas AC, Lima M, Kotoulas SC, and Dimitriou M curated the data; Angeloudi E prepared the original draft; Angeloudi E, Xanthopoulou M, Liakos A, Ioannidis P, and Gigi E reviewed and edited the manuscript; Liakos A, Ioannidis P, and Gigi E supervised the study.

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CASE REPORT

Precision at the apex: Apexification under magnification: A case report

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Abstract

BACKGROUND

Advanced materials and techniques are used to successfully manage the apexification of immature teeth with open apices. The use of mineral trioxide aggregate (MTA), bioceramic sealers, and sodium hypochlorite (NaOCl), combined with internal heating and ultrasonic activation, ensures that canals are cleaned, disinfected, and sealed properly. Magnification devices, such as dental operating microscopes (DOM), provide precise visualization for accurate material placement, while the micro apical placement system ensures void-free MTA delivery. This modern approach improves procedural outcomes, lowers iatrogenic errors, and increases long-term success in apexification, making it a dependable and predictable treatment option for immature teeth.

CASE SUMMARY

Apexification is a regenerative endodontic procedure that involves creating a calcified barrier at the apex of a nonvital tooth with an open apex. This technique is commonly used in immature teeth with necrotic pulps to ensure proper root canal sealing. Traditionally, calcium hydroxide was the preferred material, but advances have introduced bioceramic cements like MTA or Biodentine, which provide superior results with less treatment time. Apexification not only helps to maintain the tooth's structural integrity but also prevents further complications, making it an important procedure in such cases.

CONCLUSION
This case demonstrates the effectiveness of integrating advanced materials, precise irrigation protocols, and magnification tools in the apexification of immature teeth with open apices. The use of MTA created a stable apical barrier, while bioceramic sealers enhanced the seal and promoted long-term healing. NaOCl with internal heating, ultrasonic activation, and double-sided vented needles ensured thorough irrigation and disinfection, especially in complex canal anatomy.

Key Words: Bioceramics; Magnification; Mineral trioxide aggregate; Apexification; Irrigation; Case report

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Core Tip: Advanced materials and techniques are used to successfully manage the apexification of immature teeth with open apices. The use of mineral trioxide aggregate (MTA), bioceramic sealers, and sodium hypochlorite, combined with internal heating activation, ensures that canals are cleaned, disinfected, and sealed properly. Magnification devices, such as dental operating microscopes, provide precise visualization for accurate material placement, while the micro apical placement system ensures void-free MTA delivery. This modern approach improves procedural outcomes, lowers iatrogenic errors, and increases long-term success in apexification, making it a dependable and predictable treatment option for immature teeth.

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INTRODUCTION

Apexification is a specialized pediatric procedure aimed at managing immature teeth with necrotic pulp and open apices, often caused by trauma, caries, or pulp pathosis. The procedure focuses on inducing the formation of a calcified apical barrier, enabling proper sealing and long-term retention of the affected tooth[1]. Historically, calcium hydroxide was the material of choice for apexification due to its ability to stimulate the formation of hard tissue barriers[2]. However, its use necessitated a longer treatment period and multiple visits, increasing the risk of root fractures and patient noncompliance. These limitations paved the way for the adoption of bioactive materials like mineral trioxide aggregate (MTA), biodentine (Septodont, Saint-Maur-des-Fosses, France), and bioceramic putty as a superior alternative[3].

MTA has revolutionized apexification due to its exceptional biocompatibility, sealing ability, and capacity to promote cementogenesis and osteogenesis. Unlike calcium hydroxide, MTA provides predictable results in a much shorter amount of time and improves the long-term prognosis of immature teeth[4]. It creates a strong apical barrier that effectively seals the root canal system and prevents bacterial infiltration. Furthermore, its ability to promote periapical healing and stimulate hard tissue deposition has made it the preferred material for apexification procedures[5].

The use of advanced magnification devices, such as dental operating microscopes (DOMs), has increased the precision and efficacy of apexification. Magnification is essential for identifying the complex anatomy of immature teeth with open apices, which frequently exhibit irregularities or resorption[6]. The use of DOMs provides clinicians with unparalleled visualization, allowing for meticulous canal debridement, accurate apical defect assessment, and precise MTA placement. This level of precision minimizes procedural errors like overfilling and void formation, both of which can jeopardize the outcome[7].

In the context of apexification, the combination of MTA and magnification results in superior clinical outcomes. MTA's regenerative properties, combined with the increased accuracy provided by DOMs, allow for optimal apical barrier formation even in difficult cases[8]. This combination has significantly improved the predictability and success rate of apexification procedures, allowing teeth to be saved that would otherwise be extracted[9]. This case report demonstrates the successful management of an open apex with MTA under magnification, highlighting the importance of these advancements in modern pediatric and endodontic practice.

CASE PRESENTATION

Chief complaints

A 13-year-old female patient presented with severe pain and discomfort in her upper front tooth, which had persisted for the previous 2 months following trauma 2 years prior.

History of present illness

The pain was described as spontaneous, intermittent, and aggravated by biting and thermal stimuli. The patient's discomfort had progressively worsened, limiting her ability to eat and speak comfortably.

Upon further investigation, the patient stated that he had noticed occasional swelling and the presence of a sinus tract near the affected teeth in the previous few weeks. There was no history of fever or underlying illness. The patient had not taken any pain relievers before coming to the clinic.

History of past illness

The patient described a dental trauma that occurred approximately two years ago, resulting in an injury to the maxillary central incisors (teeth #11 and #21). There was no immediate treatment sought, and the teeth remained asymptomatic until two months ago, when pain began.

Personal and family history

No family history.

Physical examination

Clinical examination revealed an Ellis class IV fracture of the permanent maxillary right and left central incisor, *i.e.*, 11, 21, which was accompanied by a sinus tract near the root apex. The teeth did not respond to electric or thermal pulp sensibility tests.

Laboratory examinations

None.

Imaging examinations

A radiographic examination revealed a blunderbuss canal and a periapical lesion for both teeth.

FINAL DIAGNOSIS

Based on these findings, a periapical abscess wrt 11 and 21 was diagnosed.

TREATMENT

Following a discussion of various treatment options, it was decided to proceed with apexification using MTA wrt 11 and 21 under magnification, followed by cast post and zirconia crowns wrt 11 and 21. Rubber dam isolation was done on 11 and 21, and an access cavity was created on both teeth (Figure 1). A #80H file (Mani, Prime Dental Product Pvt. Ltd., India) (Figure 2) was used to determine the working length, while JIZAI (Mani, Prime Dental Product Pvt. Ltd., India) rotary files were used for canal instrumentation. The canal was then thoroughly cleaned with mechanical instruments and extensively irrigated with 2.5% sodium hypochlorite (NaOCl) (Bharat Chemical, India) administered through a 30 G double-sided vented needle (Master Clean, Amplemeds, India). Internal heating at 180 degrees Celsius for 5 seconds and ultrasonic activation was done to improve canal disinfection.

The canal was irrigated again with NaOCl (Bharat Chemical, India), followed by 17% EDTA to remove the smear layer. To control bleeding, a collagen sponge (Hemospon; Technew, Rio de Janeiro, Brazil) was placed in the apical third of the canal, and MTA (BioStructure, SafeEndo, India) was placed (Figure 3) incrementally using the micro-apical placement (MAP) system (Produits Dentaires SA, Vevey, Switzerland) under magnification. Each increment of MTA was condensed using a paper point (Diadent, Chungju, Korea) and a pre-fitted plugger (Meta Biomed, Chungcheongbuk-do, Korea) to form a 5 mm apical plug. Radiographs were taken to confirm MTA's precise placement at the apex (Figure 4)

After the initial set, moist cotton was placed over the MTA plug, and the patient was recalled after 24 hours. The cast post impressions were made (Figure 5) with the help of wax wrt 11 and 21. Then, after 1 week, the cast posts were cemented, a radiograph was taken (Figure 6), and crown preparations were done wrt 11 and 21, followed by crown cementation after 1 week (Figure 7).

OUTCOME AND FOLLOW-UP

At follow-up visits, the patient remained asymptomatic, and radiographs at 3, 6, and 12 months (Figure 8) revealed significant healing of the periapical lesion.

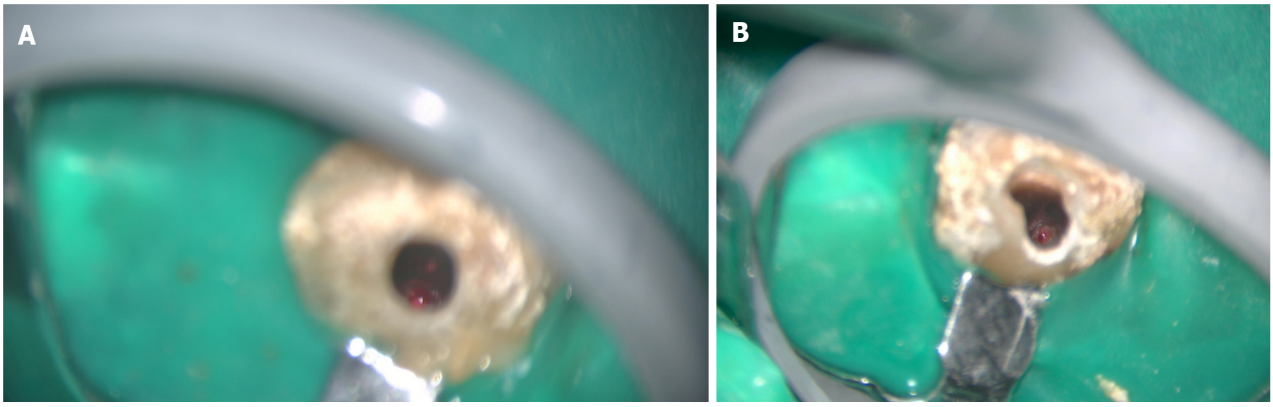


Figure 1 Shows access cavities. A: Wrt 11; B: Wrt 12.

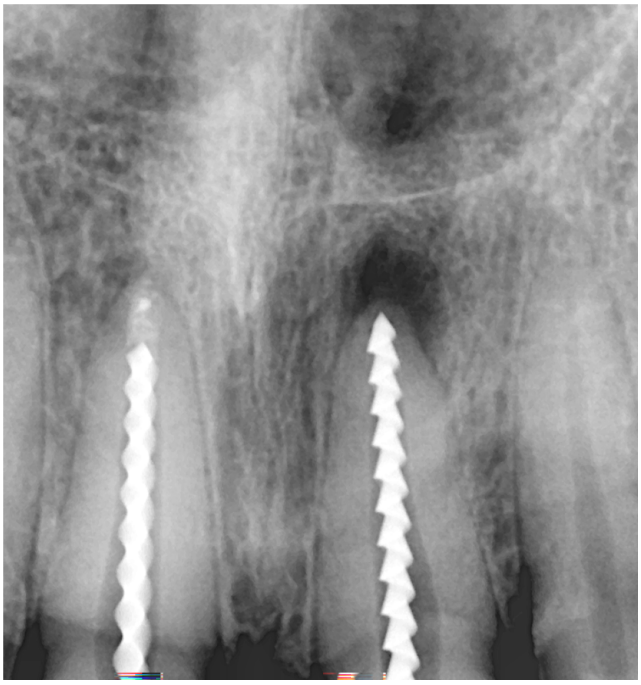


Figure 2 Shows the working length wrt 11 and 21.

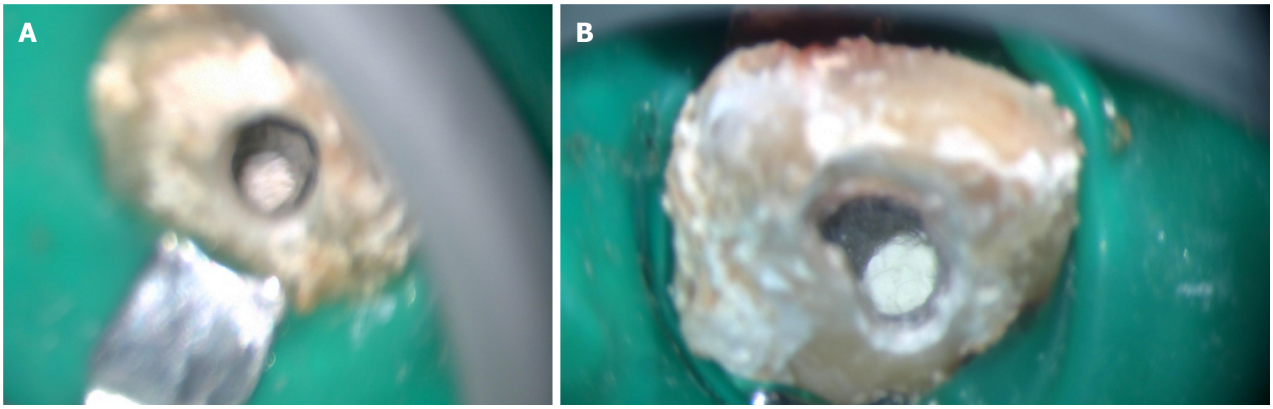


Figure 3 Shows the clinal picture of mineral trioxide aggregate placement. A: Under magnification at 16×; B: Under magnification at 20×.

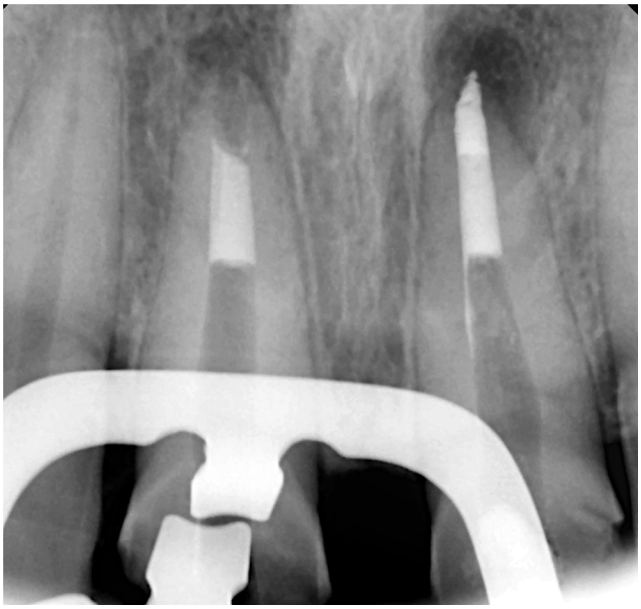


Figure 4 Shows the radiographs of 5 mm mineral trioxide aggregate plug.

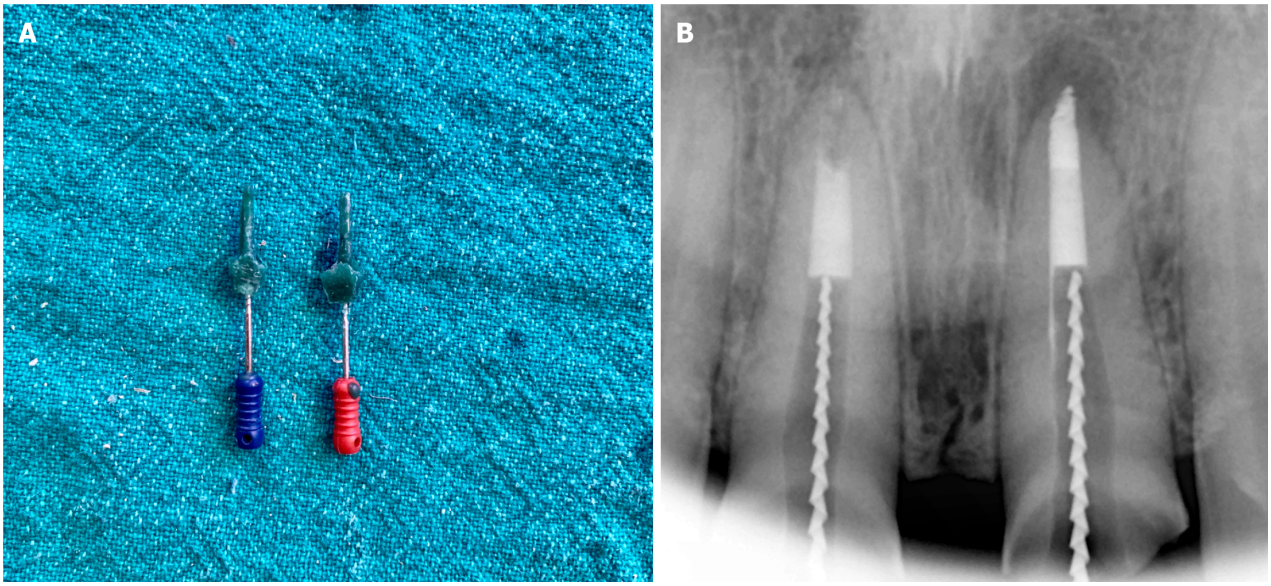


Figure 5 Shows the cast post-impression clinically and radiographically. A: Clinical pictures show the cast post impressions; B: Radiographically showing show the cast post impressions.

DISCUSSION

Apexification in immature teeth with open apices is a technically challenging procedure due to the lack of a natural apical barrier, irregular root canal anatomy, and high risk of microbial invasion[10]. This case demonstrates the use of advanced materials, precise irrigation protocols, magnification, and delivery systems, such as the MAP system, to achieve a predictable and successful clinical result[11].

MTA remains the primary apexification material, providing biocompatibility, superior sealing properties, and the ability to induce hard tissue formation. Its application in this case resulted in a strong apical barrier, which prevented reinfection and promoted periapical healing[12]. In addition to MTA, the use of a bioceramic sealer improved the seal and ensured the canal system's hermetic seal. Bioceramic sealers are well-known for their excellent adhesion, dentin bonding ability, and bioactivity, all of which contribute to long-term success by preventing microleakage and encouraging tissue regeneration[13].

Apexification relies heavily on apical seal and efficient irrigation systems. NaOCl, the gold standard irrigant, was used because of its ability to dissolve necrotic tissue while also eliminating microbial biofilms[14]. In this case, activation and internal heating of NaOCl at 180 degrees Celsius for 5 seconds under magnification increased its efficacy, allowing for thorough disinfection of the canal system, especially in the intricate apical anatomy[15]. The use of double-sided vented



Figure 6 Shows the radiograph of cast post cementation.

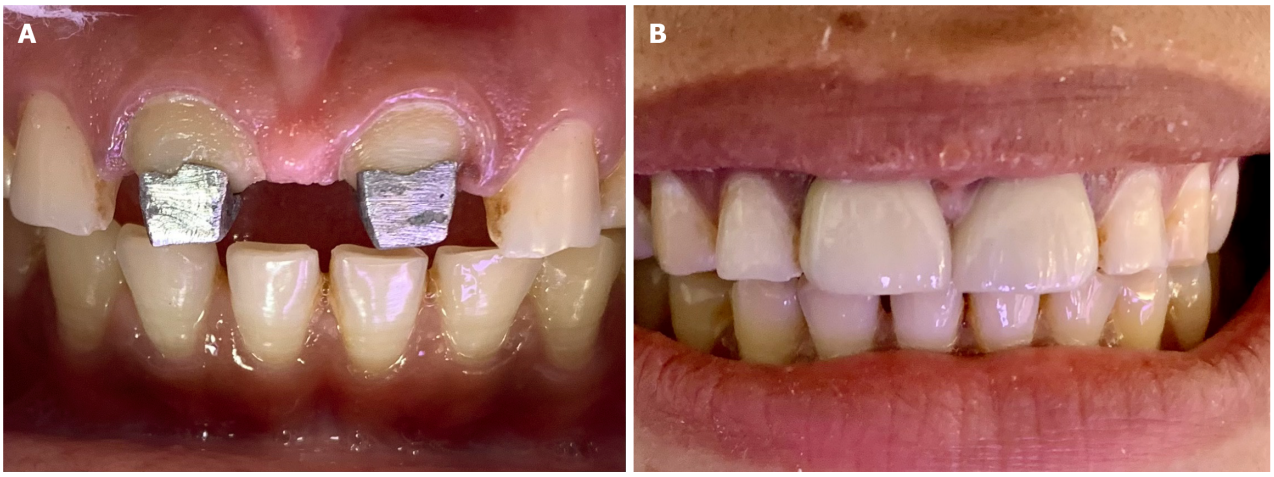


Figure 7 Shows the clinical picture. A: Cast post cementation; B: zirconia crown cementation

irrigation needles improved irrigant distribution and penetration, resulting in thorough cleaning while lowering the risk of extrusion. The combination of NaOCl, advanced irrigation techniques, and magnification ensured that all inaccessible areas were adequately debrided, resulting in an ideal environment for healing[16].

Magnification was essential throughout the procedure, allowing the clinician to see the intricate details of the canal system and apical defect. The DOM enabled the precise removal of necrotic tissue, accurate assessment of the defect, and meticulous placement of MTA[17]. The MAP system helped to deliver MTA incrementally and without voids, ensuring precise adaptation to the desired area. This method reduced procedural errors and improved the stability of the apical barrier[18].

The use of advanced materials and technologies (MTA, bioceramic sealer, NaOCl with internal heating activation, double-sided vented needles, magnification, and the MAP system) demonstrates a modern, comprehensive approach to apexification. This case demonstrates how these innovations address the challenges of managing open apices while also improving procedural efficiency and clinical outcomes, paving the way for predictable and patient-centered endodontic care[19].

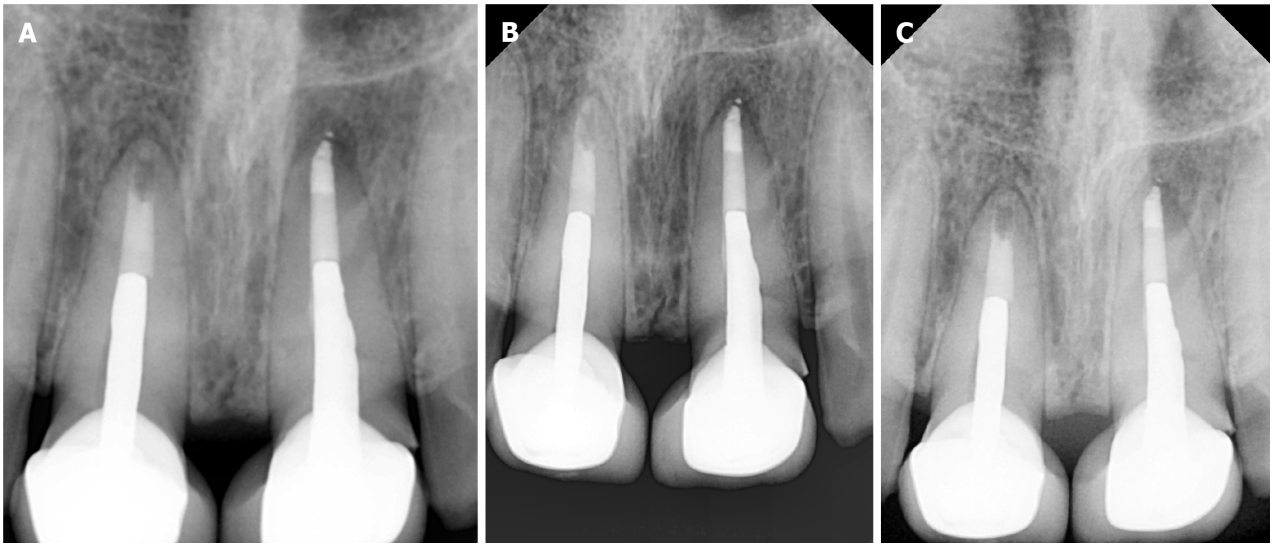


Figure 8 Shows radiograph. A: 3 months follow up; B: 6 months follow up; C: 1 year follow up.

CONCLUSION

This case demonstrates the effectiveness of integrating advanced materials, precise irrigation protocols, and magnification in the apexification of immature teeth with open apices. The use of MTA created a stable apical barrier, while bioceramic sealers enhanced the seal and promoted long-term healing. NaOCl with internal heating, ultrasonic activation, and double-sided vented needles ensured thorough irrigation and disinfection, especially in complex canal anatomy. Magnification tools, particularly the DOM, allowed for precise visualization, careful tissue removal, and accurate placement of MTA. The MAP system facilitated void-free delivery of MTA, optimizing treatment outcomes.

Overall, combining these technologies has revolutionized apexification, improving procedural efficiency and clinical success. The use of these advanced techniques reduces the risk of iatrogenic errors, enhances material adaptation, and ensures long-term tooth preservation. This case emphasizes the importance of a modern, comprehensive approach to apexification in achieving predictable and successful results.

FOOTNOTES

Author contributions: Gupta A and Bhasin P were responsible for conception and supervision; Chauhan R and Chauhan S were responsible for conception design, literature review and critical review; Chauhan R was responsible for conception data collection; Chauhan R, Gupta A and Chauhan S were responsible for conception analysis and interpretation; Sood A and Kumar H was responsible for conception write.

Informed consent statement: It is taken from the patient.

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LETTER TO THE EDITOR

Some comments on using of Web of Science Core Collection for bibliometric studies in volume 29 of the *World Journal of Gastroenterology*

Yuh-Shan Ho, Ali Ouchi

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Peer-review model: Single blind

Peer-review report's classification

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Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade B

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Abstract

The authors employed inappropriate search keywords and strategies in their published bibliometric papers within volume 29 of the *World Journal of Gastroenterology*. The comment highlights the identified issues, provides evidence, and suggests improved study methodologies. Subsequent results with more appro-priate search strategies were presented to address the shortcomings.

Key Words: Web of Science Core Collection; Front page; *World Journal of Gastroenterology*; Search keywords; Bibliometric

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Core Tip: Approximately 1% of the documents retrieved directly from searches fell outside the designated search period specified in each paper. Consequently, it can be inferred that using data directly from the Web of Science Core Collection may be inappropriate due to the potential inaccuracies introduced by this discrepancy. Findings strongly suggest that employing quotation marks (“ ”) for search keywords is essential for ensuring more accurate data analysis results in bibliometric studies. Integrating additional pertinent search keywords based on the original papers can indeed refine and enhance the precision of data analysis results in bibliometric studies. By meticulously curating the list of abbreviation terms and removing irrelevant ones, researchers can enhance the precision and accuracy of their bibliometric studies, resulting in more meaningful and insightful findings.

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TO THE EDITOR

In *World Journal of Gastroenterology*, volume 29, Web of Science Core Collection (WoSCC) was used in six different articles, entitled "Hotspots and frontiers of the relationship between gastric cancer and depression: A bibliometric study"[1], "Global trends and hotspots of treatment for nonalcoholic fatty liver disease: A bibliometric and visualization analysis (2010-2023)"[2], "Intestinal barrier in inflammatory bowel disease: A bibliometric and knowledge-map analysis"[3], "Immunological factors in cirrhosis diseases from a bibliometric point of view"[4], "Research trends on artificial intelligence and endoscopy in digestive diseases: A bibliometric analysis from 1990 to 2022"[5], and "Global trend and future landscape of intestinal microcirculation research from 2000 to 2021: A scientometric study"[6]. Table 1 shows the search strategy in each paper[1-6].

COMMENTS ON USING OF WOSCC

The WoSCC was initially designed to aid researchers in finding pertinent literature[7]. However, researchers have increasingly employed it for conducting bibliometric studies, as noted by Ho[7]. It becomes imperative to employ precise data treatment methods when utilizing this database. Particularly, approximately 1% of the documents retrieved directly from searches fell outside the designated search period specified in each paper (Table 2)[1-6]. Consequently, it can be inferred that using data directly from the WoSCC may be inappropriate due to the potential inaccuracies introduced by this discrepancy.

Despite the common convention of using quotation marks (" ") to ensure that search keywords are interpreted as phrases, Dai *et al*[2], Zhang *et al*[4], and Fu *et al*[6] did not apply this technique in their studies. For instance, Dai *et al*[2] employed the following search keywords: ((nonalcoholic fatty liver) OR (non-alcoholic fatty liver disease) OR (NAFLD) OR (MAFLD) OR (metabolic dysfunction-associated fatty liver disease) OR (metabolic associated fatty liver disease)) AND ((therapy) OR (treatment)). This formulation means ((nonalcoholic AND fatty AND liver) OR (non AND alcoholic AND fatty AND liver AND disease) OR (NAFLD) OR (MAFLD) OR (metabolic AND dysfunction AND associated AND fatty AND liver AND disease) OR (metabolic AND associated AND fatty AND liver AND disease)) AND ((therapy) OR (treatment)). It does not mean to search for phrase keywords: (("nonalcoholic fatty liver", "non-alcoholic fatty liver disease", "NAFLD", "MAFLD", "metabolic dysfunction-associated fatty liver disease", or "metabolic associated fatty liver disease") AND ("therapy" or "treatment")). Similarly, Zhang *et al*[4] used the search keywords: ((liver cirrhosis OR hepatic cirrhosis OR liver fibrosis) AND (immunologic factor OR immune factor OR immunomodulator OR biological response modifier OR biomodulator)) which means ((liver AND cirrhosis OR hepatic AND cirrhosis OR liver AND fibrosis) AND (immunologic AND factor OR immune AND factor OR immunomodulator OR biological AND response AND modifier OR biomodulator)), to signify (("liver cirrhosis" OR "hepatic cirrhosis" OR "liver fibrosis") AND ("immunologic factor" OR "immune factor" OR "immunomodulator" OR "biological response modifier" OR "biomodulator")). Lastly, Fu *et al*[6] utilized the search keywords: ((intestinal microcirculation) OR (intestinal microvascular)) which means ((intestinal AND microcirculation) OR (intestinal AND microvascular)), to represent ("intestinal microcirculation" OR "intestinal microvascular").

In the article of Dai *et al*[2], 10356 English articles and reviews were initially retrieved using appropriate search keywords enclosed in quotation marks (" "). Among these, 10316 papers (99.6% of 10356 papers) were published between 2010 and 2023. Subsequently, 9571 papers (93% of 10316 papers) were found to contain the search keywords prominently displayed on their "front page". A significant disparity emerged between the count of 11280 papers retrieved using search keywords without quotation marks (" ") and the count of 9571 papers that met the criteria for search keywords with quotation marks (" "). For the article by Zhang *et al*[4], 246 articles and reviews were initially retrieved, with 241 papers (98.0% of 246 papers) published between 2003 and 2022. Among these, 179 papers (74% of 241 papers) prominently displayed the search keywords on their "front page". A significant disparity became apparent between the count of 1604 papers retrieved using search keywords without quotation marks (" ") and the count of 179 papers meeting the criteria for search keywords with quotation marks (" "). Regarding the study conducted by Fu *et al*[6], 342 English articles and reviews were initially searched out, with 339 of these papers (99.1% of 342 papers) being published between 2000 and 2021. Subsequently, during the analysis, it was found that 306 papers (90% of 339 papers) prominently displayed the search keywords on their "front page". This observation underscores a significant difference between the initial count of 952 papers retrieved using search keywords without quotation marks (" ") and the count of 306 papers meeting the criteria for search keywords with quotation marks (" "). These findings strongly suggest that employing quotation marks (" ") for search keywords is essential for ensuring more accurate data analysis results in bibliometric studies. The discrepancy between the initial retrieval count and the count of papers meeting the specified criteria indicates the potential for misinterpretation of relevant documents when quotation marks are not utilized. Irrelevant papers might be included in a bibliometric study. Therefore, utilizing quotation marks around search keywords is

Table 1 Search strategy using the Web of Science Core Collection

Ref.	Search strategies
Liu *et al* [1]	TS = ("stomach neoplasm" OR "stomach cancer" OR "stomach tumour stomach carcinoma" OR "gastric carcinoma" OR "gastric carcinoma" OR "gastric cancer" OR "gastric neoplasm" OR "gastric tumour") AND TS = ("depression" OR "depressive disorder" OR "depressive symptom") AND PY = 2000-2022 AND DT = (article or review)
Dai *et al* [2]	TS = ((nonalcoholic fatty liver) OR (non-alcoholic fatty liver disease) OR (NAFLD) OR (MAFLD) OR (metabolic dysfunction-associated fatty liver disease) OR (metabolic associated fatty liver disease)) AND TS = ((therapy) OR (treatment)) AND LA = English AND DT = (article or review) AND PY = 2010-2023 (April 12, 2023)
Zhou *et al*[3]	TS = ("inflammatory bowel disease" OR "ulcerative colitis" OR "crohn's disease") AND TS = (intestin OR gut OR bowel) AND TS = (barrier OR integrity OR permeability) AND LA = English AND DT = article AND PY = 2001-2021
Zhang *et al*[4]	TS = ((liver cirrhosis OR hepatic cirrhosis OR liver fibrosis) AND (immunologic factor OR immune factor OR immunomodulator OR biological response modifier OR biomodulator)) AND DT = (article or review) AND PY = 2003-2022
Du *et al* [5]	TS = (("artificial intelligence" OR "AI" OR "deep learning" OR "machine learning" OR "machine intelligence" OR "computer" OR "computational intelligence" OR "neural network" OR "knowledge acquisition" OR "automatic" OR "automated" OR "feature extraction" OR "image segmentation" OR "neural learning" OR "artificial neural network" OR "data mining" OR "data clustering" OR "big data") AND ("endoscopy" OR "endoscope")) AND LA = English AND PY = 1990-2022
Fu *et al* [6]	TS = ((intestinal microcirculation) OR (intestinal microvascular)) AND LA = English AND DT = (article or review) AND PY = 2000-2021

DT: Document type; LA: Language; PY: Period; TS: Search terms.

Table 2 Comparison of results using "front page" as a filter

Ref.	TP searched out	TP in study period	TP with search keywords in their "front page"	TP from the original paper
Liu *et al*[1]	284 articles and reviews	282 articles and reviews (99.3% of 284 articles)	200 articles and reviews (71% of 282 articles)	153 articles and reviews
Dai *et al*[2]	13183 English articles and reviews	13133 English articles and reviews (99.6% of 13183 articles)	11280 English articles and reviews (86% of 13133 articles)	10829 English articles and reviews
Zhou *et al* [3]	4644 English articles	4585 English articles (98.7% of 4644 articles)	3163 English articles (69% of 4585 articles)	4482 English articles
Zhang *et al* [4]	3074 articles and reviews	3050 articles and reviews (99.2% of 3074 articles)	1604 articles and reviews (53% of 3050 articles)	2873 articles and reviews
Du *et al*[5]	4252 English documents	4197 English documents (98.7% of 4252 articles)	3820 English documents (91% of 4197 articles)	446 English documents
Fu *et al*[6]	1352 English articles and reviews	1343 English articles and reviews (99.3% of 1352 articles)	952 English articles and reviews (71% of 1343 articles)	1364 English articles and reviews

TP: Number of publications.

recommended to enhance the precision and reliability of bibliometric analyses.

In the realm of effective bibliometric studies, a prudent approach involves deeming articles without search keywords in their title, abstract, or author keywords as irrelevant to the pursued topic, as advocated by Fu and Ho[8] and emphasized by Ho[9]. In 2011, Ho's research group pioneered a groundbreaking "front page" approach, incorporating the article title, abstract, and author keywords to enhance bibliometric studies using the SCI-EXPANDED[10,11] and the SSCI[12]. A decade later, advanced search terms, specifically title (TI), abstract (AB), and author keywords (AK) within the SCI-EXPANDED and the SSCI, have been introduced and employed as the primary "front page" methodology in bibliometric studies medical-related topics[13-16]. The application of TI, AB, and AK as the "front page" has also gained traction in recent years across various bibliometric studies[17-19].

The integration of additional pertinent search keywords based on the original papers can indeed refine and enhance the precision of data analysis results in bibliometric studies. For instance, in the study by Liu *et al*[1], incorporating terms such as "stomach neoplasms", "stomach cancers", "stomach carcinoma", "gastric carcinomas", "gastric cancers", "gastric neoplasms", "depressions", "depressive disorders", and "depressive symptoms" would broaden the scope to include relevant literature on gastric cancer and depression. In the research conducted by Dai *et al*[2], additional search terms, such as "nonalcoholic fatty livers", "nonalcoholic fatter liver", "non-alcoholic fatty liver diseases", "metabolic dysfunction-associated fatty liver diseases", "metabolically associated fatty liver disease", and "metabolic-associated fatty liver diseases" would capture a more comprehensive range of studies related to treatment for nonalcoholic fatty liver disease. For the study by Zhou *et al*[3], incorporating keywords like "inflammatory bowel diseases", "inflammatory bowels disease", "ulcerative colitic", "Crohn disease", "Crohns disease", "Crohns diseases", "barriers", "permeabilities",

and "guts" would ensure the inclusion of literature relevant to a intestinal barrier in inflammatory bowel disease. In the article by Du *et al*[5], additional terms such as "computers", "computerized", "neural networks", "automatically", "automaticity", "features extraction", "feature extractions", "images segmentation", "artificial neural networks", "endoscopy", "endoscopists", "endoscopist", "endoscopes", "endoscopically", and "endoscopies" would capture studies related to artificial intelligence and endoscopy in digestive diseases. In the study conducted by Fu *et al*[6], integrating keywords like "intestinal microcirculations", "intestinal micro circulation", and "intestinal micro-vascular" would broaden the search to include literature on intestinal microcirculation research. These additional refinements contribute substantially to ensuring a thorough and precise analysis of literature within the respective fields, enhancing the comprehensiveness and accuracy of bibliometric studies.

Indeed, the abbreviation "AI" can have various meanings across different research fields, making it inappropriate as a search keyword, especially in a wide-ranging study that encompasses multiple disciplines like the one conducted by Du *et al*[5]. The term "AI" could refer to a multitude of concepts such as apnea index, arousal index, adrenal incidentaloma, apoptosis index, aspirin intolerance, allelic imbalance, apnoea index, aortic insufficiency, adrenal insufficiency, apoptotic index, adrenaline injection, angle of incidence, adventitial involvement, absolute indication, apoptotic indices, additional intervention, absorbance index, activity index, ablation index, air index, awake intubation, air insufflation, and airway interventions, among others. Thus, its usage as a search keyword could lead to ambiguity and inaccurate retrieval of relevant literature. By meticulously curating the list of abbreviation terms and removing irrelevant ones, researchers can enhance the precision and accuracy of their bibliometric studies, resulting in more meaningful and insightful findings. Moreover, in the case of Liu *et al*[1], the utilization of a limited dataset consisting of only 153 articles and reviews published over 22 years for a bibliometric study could be deemed statistically inadequate. Such a small sample size may not adequately represent the breadth and depth of the research field examining the relationship between gastric cancer and depression.

It is indeed concerning that the authors of the six papers published in the 2023 *World Journal of Gastroenterology* employed inappropriate methods for their bibliometric studies. Such practices can lead to the dissemination of misleading information to journal readers. Authors have a responsibility to ensure the accuracy and integrity of their research methods, reviewers play a crucial role in identifying and highlighting any mistakes or shortcomings in the manuscripts they review, and journal editors must exercise vigilance in assessing the quality and validity of articles submitted for publication.

CONCLUSION

As highlighted by Ho[20], research serves as a pathway to truth, and researchers need to strive for accuracy and innovation in their work. Merely duplicating the same mistakes without making efforts to improve research methods does not contribute positively to the advancement of knowledge. Therefore, it is imperative for all stakeholders involved in the publication process, including authors, reviewers, and editors, to uphold rigorous standards of scientific integrity and to actively work towards improving the quality of research published in academic journals.

FOOTNOTES

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LETTER TO THE EDITOR

Advancing dental precision: The synergy of magnification and artificial intelligence

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Abstract

The article by Chauhan *et al* highlights the transformative potential of magnification tools in improving precision and outcomes across various dental specialties. While the authors discuss the advantages of magnification, they do not address the potential integration of artificial intelligence (AI) with magnification devices to further enhance diagnostic and therapeutic efficiency. This letter explores the synergy of AI with magnification tools, emphasizing its applicability in image-guided diagnostics, workflow optimization, and personalized treatment planning. The integration of AI and magnification also paves the way for personalized, data-driven treatment strategies, marking a significant evolution in dental care. However, it is important to acknowledge the limitations and challenges associated with AI, such as data privacy concerns, algorithmic biases, and the need for robust validation before clinical implementation. This discussion underscores the need for interdisciplinary research to realize this potential.

Key Words: Artificial intelligence; Dental magnification; Diagnostic imaging; Workflow optimization; Personalized treatment planning; Dentistry

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Core Tip: Magnification tools have revolutionized dentistry, but their integration with artificial intelligence (AI) represents the next paradigm shift. This letter highlights the potential of AI-enhanced magnification for diagnostics, workflow optimization, and personalized treatment planning. AI algorithms can analyze magnified images for early diagnosis, streamline procedures with real-time feedback, and provide tailored treatment insights based on patient-specific data. These innovations promise to elevate precision, efficiency, and outcomes in dental care, encouraging interdisciplinary advancements to fully realize this synergy.

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TO THE EDITOR

I read with great interest the article "Magnification: The Game Changer in Dentistry" by Chauhan *et al*[1]. The authors present a compelling review of the applications of magnification in dentistry, spanning specialties such as endodontics, periodontics, and prosthodontics. The emphasis on improved visual acuity, ergonomic benefits, and enhanced procedural outcomes is well-founded. However, the article does not explore the potential integration of artificial intelligence (AI) with magnification devices, which could revolutionize the future of dentistry. Allow me to elaborate on this emerging frontier.

Ai-Assisted diagnosis and amplification

Combining AI algorithms with magnification tools can significantly enhance diagnostic capabilities[2,3]. For instance, magnification devices equipped with real-time AI image analysis[4] could aid in identifying early-stage carious lesions, fractures, or pulp stones with unparalleled precision. Advanced deep learning models can be integrated into dental microscopes to analyze high-resolution magnified images, flagging potential abnormalities for the clinician to review[5]. This technology has the potential to reduce diagnostic errors, streamline chairside decision-making, and facilitate minimally invasive interventions.

Furthermore, AI systems can continuously learn and adapt from a database of clinical cases, improving their diagnostic accuracy over time[6,7]. These systems can also provide quantifiable metrics, such as lesion dimensions or bone density levels, assisting clinicians in monitoring disease progression or treatment efficacy. The integration of AI with magnification thus not only augments the clinician's expertise but also ensures evidence-based diagnostics tailored to individual patient needs. However, it is important to note that AI-assisted diagnostics are not without limitations. Challenges such as data privacy, algorithmic biases, and the need for extensive validation in diverse clinical settings must be addressed to ensure reliable and equitable implementation.

Workflow optimization through AI and amplification

Magnification devices paired with AI can optimize workflow by providing augmented reality overlays directly in the clinician's field of view[2]. For example, during endodontic procedures, AI could highlight canal anatomy or suggest the optimal tool trajectory based on real-time visual feedback from the magnified field[8]. Furthermore, machine learning algorithms can predict procedural outcomes, helping clinicians plan and execute treatments with greater confidence. Such tools could be especially useful in microsurgical periodontics, where precision directly impacts patient recovery and aesthetic results[9].

In addition, AI-integrated magnification tools can automate repetitive tasks, such as calculating measurements or tracking procedural steps. For example, during implant placement, AI can guide angulation and depth, minimizing the risk of errors and ensuring better osseointegration[10]. These features can significantly reduce procedure times while maintaining high levels of accuracy, thereby enhancing both clinical efficiency and patient satisfaction. Nevertheless, the reliance on AI for workflow optimization raises concerns about over-automation, which may reduce clinician autonomy and critical thinking. Additionally, the integration of AI into clinical workflows requires significant investment in infrastructure and training, which may not be feasible for all practices.

Individualized treatment planning

AI-enhanced magnification devices can also support personalized treatment strategies[11]. By integrating patient data, such as 3D imaging and medical history, AI systems could provide tailored insights during procedures. For example, in prosthodontics, AI could guide crown preparation and seating by analyzing marginal gaps in real-time, ensuring a better fit and longer restoration lifespan[12]. This fusion of AI and magnification could lead to a new era of precision dentistry, improving both patient outcomes and clinician satisfaction.

Moreover, AI can simulate potential treatment outcomes based on patient-specific parameters, enabling clinicians to make informed decisions. For instance, in orthodontics, AI-driven magnification could visualize tooth movement trajectories and suggest optimal adjustments to achieve desired results efficiently[11,13]. This capability not only enhances clinical precision but also fosters better communication with patients, as they can visualize expected outcomes

before undergoing treatment. However, the use of AI in personalized treatment planning must be approached with caution, as it relies heavily on the quality and diversity of the data used to train the algorithms. Biases in training data could lead to suboptimal or inequitable treatment recommendations.

Limitations and challenges of AI in dentistry

While the integration of AI and magnification tools holds immense promise, it is crucial to acknowledge its limitations and challenges. First, AI systems require large, high-quality datasets for training, which may be difficult to obtain due to privacy concerns and data-sharing restrictions[11]. Second, algorithmic biases can arise if the training data is not representative of diverse patient populations, potentially leading to inequitable outcomes[13]. Third, the clinical validation of AI systems is essential to ensure their safety and efficacy, but this process can be time-consuming and resource-intensive [11]. Finally, the adoption of AI in dentistry may face resistance from clinicians who are skeptical of its reliability or concerned about its impact on their professional autonomy[10,11]. Addressing these challenges will require collaborative efforts among researchers, clinicians, and policymakers to establish robust frameworks for AI development, validation, and implementation.

CONCLUSIONS

While magnification tools have already proven to be a game changer in dentistry, their integration with AI represents the next evolutionary step. AI-driven innovations could complement the capabilities of magnification, providing clinicians with real-time diagnostics, workflow enhancements, and personalized care solutions. However, the limitations and challenges associated with AI must not be overlooked. A balanced approach that leverages the strengths of AI while addressing its shortcomings is essential to ensure its successful integration into dental practice. As technology advances, interdisciplinary research and development efforts should focus on realizing this synergy to further elevate the standard of dental care.

FOOTNOTES

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LETTER TO THE EDITOR

Recurrent femoral stem fractures in Dorr A femurs: Lessons learned and a call for alternative strategies

Carlos M Lucero, Juan Bautista Luco, Agustin Albani Forneris, Martin A Buttaro

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Abstract

We report a unique case of bilateral femoral stem fractures in a patient with Dorr A femoral morphology, underscoring the need for a critical reassessment of implant selection strategies. The initial failure involved a cemented revision stem placed using the cement-within-cement technique combined with an extended trochanteric osteotomy (ETO). A second revision was subsequently performed using a cortical window osteotomy and a distally fixed uncemented stem, which resulted in successful recovery. A similar approach was used to treat a subsequent contralateral stem fracture, also with favorable outcomes. This case emphasizes three key considerations: First, that standard-length cemented stems may lead to oversizing and increased stress concentration in Dorr A femurs with narrow canals; second, that ETO may compromise femoral integrity and contribute to implant failure; and third, that cortical window osteotomy enables safer implant removal and reimplantation. Based on these findings, we advocate for an individualized approach to implant selection that may include cemented short stems, uncemented short stems, or modular solutions depending on femoral anatomy and patient-specific factors, and we encourage further investigation into optimal fixation strategies for patients with Dorr A femoral morphology.

Key Words: Exeter stem; Femoral stem breakage; Femoral osteotomy; Total hip arthroplasty; Case report

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Core Tip: This case highlights bilateral femoral stem fractures in a patient with Dorr A femoral morphology, raising concerns about the mechanical reliability of cemented fixation in such cases. Through successful management with cortical window osteotomy and uncemented distal fixation, we emphasize the importance of tailoring revision strategies to femoral anatomy. Our experience reinforces the need to reconsider implant selection in Dorr A femurs to prevent recurrent failure.

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TO THE EDITOR

Following our previously published case report on femoral stem refracture in a Dorr A femur[1], we find ourselves revisiting our own conclusions in light of an unexpected recurrence in the same patient. This reinforces key considerations regarding implant selection and revision strategies in this particular femoral morphology.

In our original publication, we described a refracture of a cemented femoral stem in a Dorr A femur after revision surgery involving extended trochanteric osteotomy (ETO) and a cement-within-cement (CWC) technique[1]. The failure of the revised stem led us to perform a second revision using a cortical window osteotomy, allowing safe extraction of the distal stem fragment and cement, followed by implantation of a distally fixed uncemented stem. The patient had an uneventful recovery, reinforcing the efficacy of this approach[1,2].

Recently, however, the same patient presented with a femoral stem fracture in the contralateral hip, further challenging the reliability of cemented stems in Dorr A femurs (Figure 1) With the knowledge gained from our prior experience, we opted for the same approach: A cortical window osteotomy for safe removal of the fractured stem and cement, followed by the implantation of a distally fixed uncemented stem. This method once again allowed direct visualization, ensured a controlled cement removal process, and minimized damage to the femoral cortex (Figure 2)[3]. The patient's postoperative recovery was uneventful, with full weight-bearing resumption within weeks.

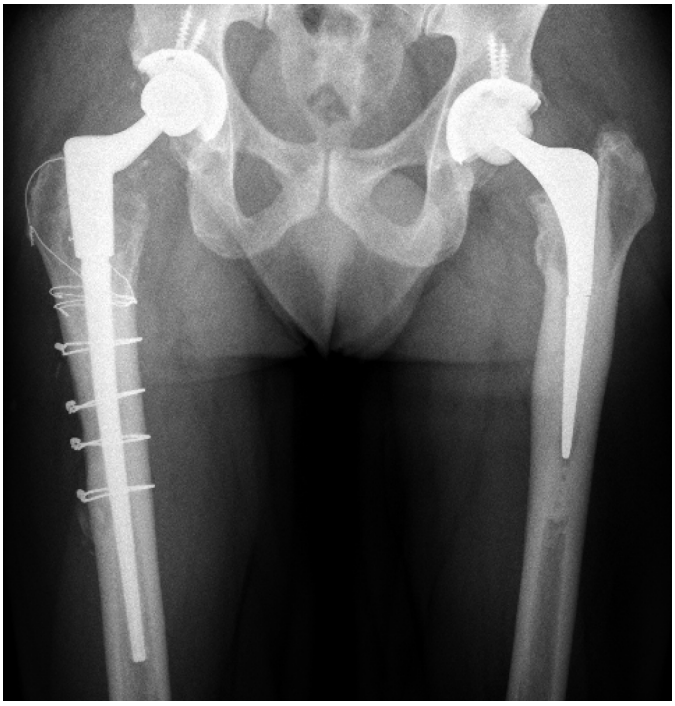


Figure 1 Anteroposterior X-ray of both hips, 13 years after left hip surgery, showing a fracture at the proximal-middle third of the left femoral stem.

Revisiting our key considerations

Cemented stems in Dorr A femurs require careful consideration: The high cortical thickness and narrow diaphyseal canal characteristic of Dorr A femurs may lead to mechanical mismatch with standard-length cemented stems, increasing the risk of cement mantle thinning and stress concentration at the stem-body junction[1-4]. However, this does not

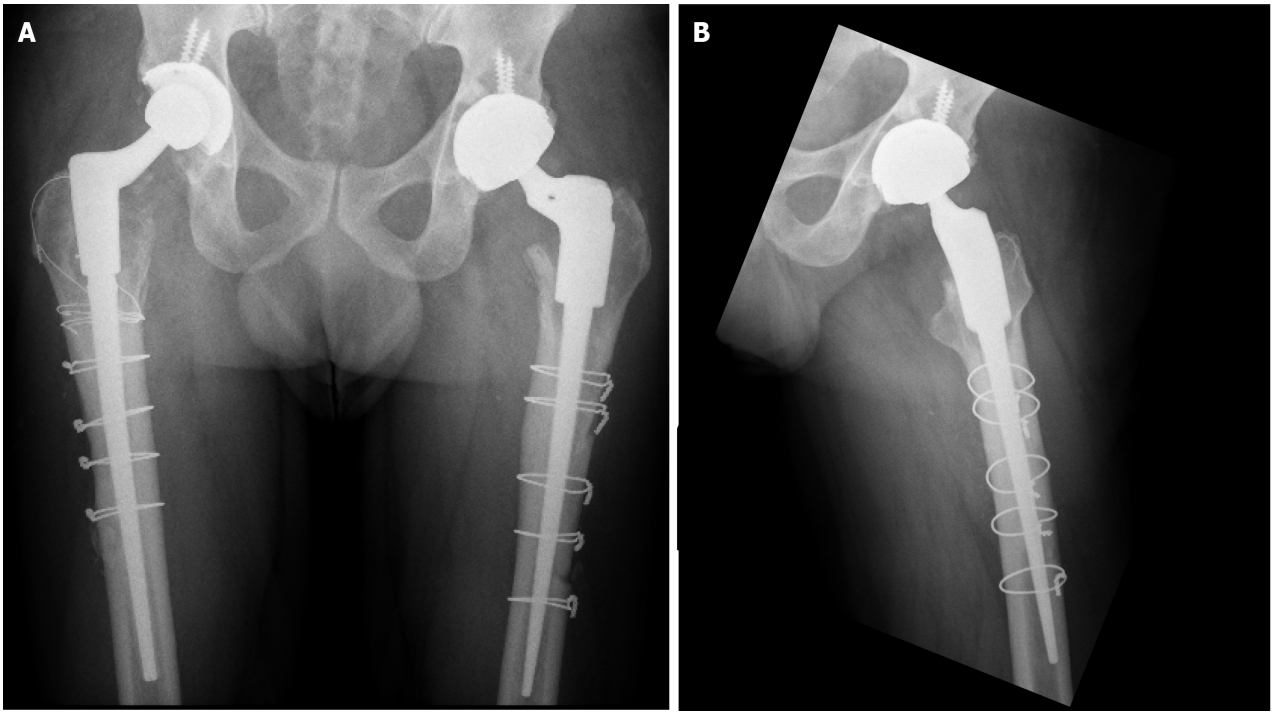


Figure 2 Anteroposterior and lateral X-ray 2 months after revision surgery, in which the correct position of the femoral implant and consolidation of osteotomy are shown. A: Orthostatic; B: Lateral.

preclude cemented fixation altogether. When appropriately sized, such as with short or specially designed cemented stems, successful outcomes have been reported even in narrow canals. The key lies in tailoring the implant choice to the patient's specific femoral morphology.

ETO may increase mechanical risk in Dorr A femurs: Although widely used in revision procedures, ETO can compromise the femoral structure—particularly in patients with a dense cortex and limited canal diameter—potentially predisposing to refracture[5]. Our case reinforces the need for alternative extraction techniques in such femoral types.

Cortical window osteotomy is a viable revision strategy: This technique allowed for direct visualization and safe extraction of the fractured stem and cement while minimizing additional cortical damage. It also facilitated accurate implant placement and may be preferred over ETO in select patients, especially those with stiff, narrow femurs[2,3].

Implications for future practice

Our experience suggests that fixation strategies in Dorr A femurs should not adopt a one-size-fits-all approach. Rather than categorically avoiding cemented stems, surgeons should carefully evaluate canal geometry, patient age, bone quality, and mechanical demands. Cemented short stems or stems specifically designed for narrow femoral canals may be appropriate in older or low-demand patients. Conversely, distally fixed uncemented stems or short cementless stems may offer better outcomes in younger or more active individuals, provided they achieve stable metaphyseal fixation. This case underscores the importance of individualized implant selection and highlights the need for further research into fixation principles specifically tailored to the unique characteristics of Dorr A femoral anatomy.

FOOTNOTES

Author contributions: Lucero CM served as the principal author of both the current study and the previous related work; Luco JB was responsible for obtaining informed consent and organizing the relevant case documentation; Forneris AA contributed as a secondary writer and assisted in patient follow-up; Buttero MA acted as the senior author, overseeing the project and making the necessary revisions.

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