ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 November 26; 12(33): 6580-6663

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents Thrice Monthly Volume 12 Number 33 November 26, 2024

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 33 November 26, 2024

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LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 33 November 26, 2024

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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PUBLICATION DATE
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World J Clin Cases 2024 November 26; 12(33): 6580-6586

DOI: 10.12998/wjcc.v12.i33.6580

ISSN 2307-8960 (online)

EDITORIAL

Influence of sarcopenia and frailty in the management of elderly patients with acute appendicitis

Pietro Fransvea, Maria Michela Chiarello, Valeria Fico, Maria Cariati, Giuseppe Brisinda

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Yin Z

Received: March 14, 2024

Revised: August 6, 2024

Accepted: August 14, 2024

Published online: November 26, 2024

Processing time: 196 Days and 12.2 Hours

Pietro Fransvea, Valeria Fico, Giuseppe Brisinda, Emergency and Trauma Surgery Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma 00168, Italy

Maria Michela Chiarello, Department of Surgery, Provincial Health Authority, Cosenza 87100, Italy

Maria Cariati, Department of Surgery, Provincial Health Authority, Crotone 88900, Italy

Giuseppe Brisinda, Translational Medicine and Surgery, Catholic School of Medicine, Roma 00168, Italy

Co-first authors: Pietro Fransvea and Maria Michela Chiarello.

Corresponding author: Giuseppe Brisinda, MD, Professor, Surgeon, Emergency and Trauma Surgery Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, No. 8 Largo Agostino Gemelli, Roma 00168, Italy. gbrisin@tin.it

Abstract

In developed countries, the average life expectancy has been increasing and is now well over 80 years. Increased life expectancy is associated with an increased number of emergency surgical procedures performed in later age groups. Acute appendicitis is one of the most common surgical diseases, with a lifetime risk of 8%. A growing incidence of acute appendicitis has been registered in the elderly population and in the oldest groups (> 80 years). Among patients > 50-year-old who present to the emergency department for acute abdominal pain, 15% have acute appendicitis. In these patients, emergency surgery for acute appendicitis is challenging, and some important aspects must be considered. In the elderly, surgical treatment outcomes are influenced by sarcopenia. Sarcopenia must be considered a precursor of frailty, a risk factor for physical function decline. Sarcopenia has a negative impact on both elective and emergency surgery regarding mortality and morbidity. Aside from morbidity and mortality, the most crucial outcomes for older patients requiring emergency surgery are reduction in function decline and preoperative physical function maintenance. Therefore, prediction of function decline is critical. In emergency surgery, preoperative interventions are difficult to implement because of the narrow time window before surgery. In this editorial, we highlight the unique aspects of acute appendicitis in elderly patients and the influence of sarcopenia and frailty on the results of surgical treatment.

Key Words: Acute appendicitis; Appendectomy; Elderly; Frailty; Sarcopenia

Core Tip: The global proportion of older subjects is steadily increasing. This is associated with an increased number of emergency surgical procedures performed in this age group. Acute appendicitis is one of the most common surgical diseases, with a lifetime risk of 8%. A growing incidence of acute appendicitis has been registered in the elderly population and in the oldest age group (> 80 years). In this editorial, we highlight the characteristics of acute appendicitis in elderly patient and the influence of sarcopenia and frailty on the results of surgical treatment.

Citation: Fransvea P, Chiarello MM, Fico V, Cariati M, Brisinda G. Influence of sarcopenia and frailty in the management of elderly patients with acute appendicitis. *World J Clin Cases* 2024; 12(33): 6580-6586
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6580.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6580

INTRODUCTION

The global proportion of older subjects is steadily increasing[1]. By convention, a chronological age equal to or greater than 65 years is considered elderly. A cut-off of 75 years or older has recently been suggested based on improvements in physical function over the past 20 years[2]. In fact, in many countries, especially in developed ones, the average life expectancy has increased and far exceeds 80 years[1]. This is associated with an increased number of emergency surgical procedures performed in this age group[3-5].

Acute appendicitis is one of the most common surgical diseases, with a lifetime risk of 8%[6-8]. A growing incidence of acute appendicitis has been registered in the elderly population and in the oldest age group (> 80 years)[8-10]. Among patients > 50-year-old who present to the emergency department for acute abdominal pain, 15% have acute appendicitis [11].

In this editorial, we highlight the unique aspects of acute appendicitis in elderly patients and the influence of sarcopenia and frailty on the results of surgical treatment.

CHARACTERISTICS OF ACUTE APPENDICITIS

Emergency surgery for acute appendicitis in the elderly is challenging[4]. Some important aspects must be considered. The first aspect is the difficulty of diagnosis because elderly patients may not present the characteristic clinical signs of acute appendicitis[12]. There is still controversy on whether the presentation of acute appendicitis in the elderly patients significantly differs from those in the younger age groups[13]. Signs of peritonitis may become evident with reduced peristalsis and severe tenderness[14,15]. Furthermore, as age increases, the ability to perceive pain decreases, and due to reduced thermoregulatory response and abnormalities in the response to endogenous pyrogens, approximately 30% of patients aged 65 years or older with acute infection show a lower febrile response[15].

Second, the incidence of complicated acute appendicitis is higher in elderly patients[11,16]. The prevalence of complicated appendicitis increases with age. If the prevalence is approximately 20% in patients under 40 years of age, this increases up to 37% in patients between 40 years and 64 years of age to reach higher than 55% in patients over seventy and higher than 70% in patients over 80[11,17]. However, acute appendicitis is not a progressive disease[12]. Complicated and uncomplicated forms of appendicitis are two distinct entities with different pathophysiology[14]. Gangrene with transmural necrosis, perforation, the presence of appendicoliths, abdominal abscess and/or diffuse peritonitis characterize complicated acute appendicitis, while suppurative or phlegmonous changes prevail in uncomplicated forms.

Third, the use of abdominal computed tomography (CT)-scan to make the diagnosis is frequent in elderly[18]. This is the most accurate method for distinguishing uncomplicated from complicated appendicitis[19,20]. The increased use of CT in elderly patients leads to a decrease in negative appendectomy rates by 10%. The frequency of negative appendectomy is up to 16% in younger patients[21]. The complication rate in elderly patients with negative appendectomy was higher than in younger patients (25% *vs* 3%, $P < 0.05$)[22]. Considering that the complication rate in elderly patients with negative appendectomy is higher than in younger patients, the preoperative diagnosis in these patients should be as accurate as possible.

A fourth aspect to consider is the time elapsed from hospitalization until surgery. Typically, up to approximately 72% of elderly patients are operated on more than 12 h after admission compared to approximately 35% of younger patients[9,23]. Furthermore, 37% of elderly patients are operated on more than 24 h after admission, although this interval does not appear to cause any increase in postoperative complications[24]. However, it is important to remember that acute appendicitis is a time-dependent disease[25]. Source control within 6 h of abdominal sepsis onset was associated with a reduced risk-adjusted odds of 90-day mortality. In elderly patients with acute appendicitis, once operation is indicated,

we suggest performing appendectomy as soon as possible. Prioritizing the rapid identification of septic foci and initiation of source control interventions can reduce the number of avoidable deaths among patients with sepsis.

In the elderly patient, the best treatment for acute appendicitis is surgery[17,26,27]. Recent meta-analyses have shown that appendectomy seems even more effective than non-operative treatments. The finding of a 20% recurrence rate in patients > 80 years of age undergoing non-surgical treatment suggests that antibiotics may be a treatment option only in selected patients with uncomplicated appendicitis[28]. Anyway, a frail patient cannot tolerate repeated septic episodes.

Laparoscopic appendectomy is the standard of care in acute appendicitis. Several clinical studies have demonstrated the advantages of laparoscopic appendectomy over open surgery. In meta-analysis on the elderly population, mortality, postoperative complications, and length of hospital stay were significantly lower when using the laparoscopic approach *vs* an open surgery[29,30]. Despite the advantages of the minimally invasive technique, there is an increased risk of conversion from laparoscopy to open appendectomy in elderly patients[31]. The rate of laparoscopies performed on older adults varies significantly, ranging from 19.3% to 67%[29,32]. The most common cause of conversion is peri-appendiceal infiltration/an inflammatory mass, which makes sectioning of the appendix difficult and requires less or more extensive ileocolic resection.

Furthermore, older patients have an increased risk of appendiceal neoplasm. A recent study on 989 patients undergoing emergency appendectomy showed an overall incidence of appendiceal neoplasm of 9.3% (92 patients). The rate of appendiceal neoplasm increased with age (3.8% in younger patients and 13.0% in patients between 40 years and 89 years). In the study, appendectomy was performed in all cases. The conversion rate was significantly higher in patients with appendiceal neoplasm (21.6% *vs* 6.7% in acute appendicitis, $P < 0.001$)[33].

Predicting outcomes in emergency surgery is challenging due to the heterogeneous mix of patients, pathologies, indications and urgency of surgery. Increasingly, emergency laparotomies are performed on older patients with complex medical conditions who subsequently encounter increased postoperative morbidity and mortality[34]. In appendectomy, mortality varies from 0.74% to 8% in the elderly and increases with age, while it is 0.04%-1% in the general population[21,26]. Advanced age adversely affects clinical diagnosis, the stage of the disease and outcomes. Late presentation, delayed diagnosis, presence of perforation and co-morbidities are associated with poor outcome from surgery in elderly patients.

Postoperative complications can affect up to 46.2% of elderly patients compared to 9.3% of younger patients[31]. Surgical site infection occurs in 9.0%-15.4% of elderly patients, compared to 2.6%-3.7% of younger patients[35]. In elderly, independent factors for postoperative complications include anemia, a history of heart disease, chronic renal failure, and open appendectomy surgery[16]. A recent meta-analysis showed that elderly patients have an increased risk of complicated appendicitis (RR, 2.38; 95%CI: 2.13, 2.66), peritonitis (RR, 1.88; 95%CI: 1.36, 2.59), and conversion from laparoscopic to open appendectomy (RR, 3.02; 95%CI: 2.31, 3.95). In addition, the risk of overall postoperative complications (RR, 2.59; 95%CI: 2.19, 3.06), intra-abdominal abscess (RR, 1.84; 95%CI: 1.15, 2.96) and wound infection (RR, 3.80; 95%CI: 2.57, 5.61) was higher among the elderly[31].

SARCOPENIA AND FRAILTY

In the elderly, postoperative complications are also influenced by sarcopenia[10,36]. Sarcopenia must be considered a precursor of frailty, a risk factor for physical function decline[37]. Sarcopenia has shown a negative impact on both elective and emergency surgery regarding mortality and morbidity[38-41]. Aside from morbidity and mortality, the most crucial outcomes for older patients requiring emergency surgery are reduction in function decline and preoperative physical function maintenance[42]. Therefore, predicting the decline in functionality is crucial. It should be noted, however, that preoperative interventions are difficult to implement in emergency/urgent conditions due to the narrow time window before surgery[41].

A recent observational study of 610 patients undergoing emergency laparotomy showed that sarcopenia and myosteatosis were both associated with increased risk of morbidity, 30-day and 1-year mortality[40].

Sarcopenia is a morbid condition that directly involves the skeletal muscles with repercussions at a multisystem level [43]. Although with wide individual variability, approximately 1%-2% of muscle mass is lost every year after the fifth decade of life for a total reduction of 30%-50% by the age of 80. It is a preventable but chronic and reversible process.

Sarcopenia has been used as a prognostic tool to identify patients at risk for complications and adverse events in the postoperative period[24,44]. In this scenario, it has been documented that geriatric patients with lower body mass index, reduced muscle area, and marked sarcopenia detected by CT-scan tend to have an increased risk of complicated acute appendicitis[45].

Clinically, sarcopenia induces a reduction in muscular strength, both dynamic and static, with an increased risk of functional decline, disability and frailty, a reduction in the ability to maintain balance with an increased risk of falls and fractures, consequences on bone trophism, thermoregulation, basal energy production, regulation of body composition, and glucose homeostasis[46]. Muscle trophism is the consequence of a balance between anabolic and catabolic stimuli. In the elderly, a prevalence of the catabolic state is documented, which becomes predominant if comorbidities occur. In these cases, the muscle mass also suffers the effects of the general catabolic state in which the organism finds itself.

The European Working Group on Sarcopenia in Older People recommends the simultaneous presence of loss of muscle mass associated with reduced muscle strength or performance for the diagnosis of sarcopenia[46,47]. To evaluate these criteria, there are several investigations that differ in terms of sensitivity[48,49]. This variability accounts for the different prevalence percentages of sarcopenia found across various studies. Several biochemical markers have shown a strong association with sarcopenia, including low levels of vitamin D, IGF-1 and high levels of parathyroid hormone, C-reactive protein, TNF-α, and IL-6[50]. In addition to these, other indices significantly correlate with reduced muscle mass and

performance. However, a specific and sensitive marker of sarcopenia that allows for rapid and early diagnosis has not yet been identified.

Frailty is the most problematic expression of aging characterized by a state of vulnerability to any stressful event. It is due to the reduced homeostatic reserve of the organism which follows the functional decline of various physiological systems. The repercussions on the socio-health level are notable. In fact, it has been demonstrated that frailty is associated with an increased risk of negative outcomes, such as disability, hospitalization and death[51,52]. Frailty in the emergency surgical patient has been recently characterized in both older and younger populations[53]. Frailty can be difficult to identify in emergency settings[54]. Fusario *et al*[55] showed that the Emergency Surgery Frailty Index score is a useful and simple prognostic marker for frailty status in surgical elderly patients. The score may support the surgeon in decision for an adequate healthcare plan and preoperative preparation.

An increased risk of postoperative complications in elderly patients undergoing emergency laparotomy is usually associated with an increased frailty score[56]. These patients have more frequent admission to the intensive care unit and an increased length of stay. Furthermore, the mortality rate in frail patients was higher (17%) compared to less than 1% in non-frail patients (P = 0.01)[56]. In a study of 5728 older adults undergoing appendectomy, frail patients were documented to have higher mortality (frail 1.0% *vs* non-frail 0.3%, P = 0.001) and severe complications (14.2% *vs* 8.0%, P < 0.0001). In multivariable logistic regression, frailty was associated with increased mortality (OR 3.34; 95%CI: 1.28-8.66), severe complications (OR 1.51; 95%CI: 1.17-1.93) and discharge to facility (OR 2.80; 95%CI: 2.00-3.93)[57].

On the other hand, it has been noted that a modified Frailty Index and a Brief Geriatric Assessment do not correlate with prolonged hospitalization or higher risk for postoperative complications after appendectomy in elderly patients[52]. In this scenario, the evaluation of sarcopenia status can add further information regarding the general condition of the patient that could make the therapeutic choice personalized.

Based on the current knowledge, most studies are performed on samples of patients enrolled for elective, scheduled surgery, which allows optimizing the patient in the preoperative period[58,59].

In an emergency setting, the situation appears more complex, with patients in whom it has not been possible to carry out an in-depth preoperative evaluation, often with the inflammatory/septic process causing greater general fragility[36,38]. As highlighted in recent studies, sarcopenic patients undergoing surgery are expected to be at higher risk of complications than patients with normal muscle mass. Therefore, in this setting, sarcopenia evaluation is a potential parameter that could support the surgeon during the decision-making process[36,60]: an older and sarcopenic patient cannot tolerate a prolonged septic status, so in these cases a surgical approach should be preferred over a conservative treatment in all type of acute appendicitis. In this context, the use of artificial intelligence could be useful[61].

CONCLUSION

The diagnosis of acute appendicitis in the elderly remains a clinical challenge. The elderly patient presents a diagnostic challenge. The presentation of the disease may be atypical in relation to the physiological changes due to age and a wider variety of conditions for differential diagnosis. Comorbidities and their associated polypharmacy affect the appropriate choice of imaging modality. In these patients, CT-scan is often performed for diagnosis, even in emergency settings. In such conditions, the total psoas muscle index and total psoas muscle area can be easily calculated on CT-scan. The gold standard approach is surgical treatment, although not all elderly patients may be suitable for surgery. It is therefore essential that the treatment plan be organized for each individual case, also in relation to the skills of the individual institution or surgeon.

FOOTNOTES

Author contributions: Fransvea P, Chiarello MM and Brisinda G designed the research; Fransvea P, Fico V and Cariati M performed the research; Fransvea P and Fico V analyzed the data. All authors wrote and approved the final manuscript.

Conflict-of-interest statement: Dr. Brisinda has nothing to disclose.

Country of origin: Italy

ORCID number: Pietro Fransvea 0000-0003-4969-3373; Maria Michela Chiarello 0000-0003-3455-0062; Valeria Fico 0000-0003-1619-4164; Maria Cariati 0000-0002-3278-2567; Giuseppe Brisinda 0000-0001-8820-9471.

S-Editor: Lin C
L-Editor: Filipodia
P-Editor: Chen YX

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6587-6590

DOI: 10.12998/wjcc.v12.i33.6587

ISSN 2307-8960 (online)

EDITORIAL

Evaluation of the mental health of COVID-19 patients discharged from the intensive care unit

Elif Sarac

Specialty type: Psychology, Social

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Adam CA

Received: April 26, 2024
Revised: June 3, 2024
Accepted: June 25, 2024
Published online: November 26, 2024
Processing time: 153 Days and 14.4 Hours

Elif Sarac, Ministry of National Defense, General Directorate of Management Services, Ankara 06000, Türkiye

Corresponding author: Elif Sarac, PhD, Researcher, Ministry of National Defense, General Directorate of Management Services, Bilkent, Ankara 06000, Türkiye. sarac.elf@gmail.com

Abstract

In this editorial, I address the mental health status of patients who have been discharged from intensive care units (ICUs) after battling coronavirus disease 2019 (COVID-19). An ICU admission is generally a stressful experience, and for severe COVID-19 survivors prolonged treatment in the ICU can lead to significant psychological consequences. These individuals may experience psychiatric distress, including symptoms such as insomnia, anxiety, depression, and even post-traumatic psychological issues. Research indicates that during the first 6 months to 1 year following an ICU stay, nearly one-third of survivors exhibit symptoms similar to those of depression and post-traumatic stress disorder. Several factors may have contributed to the development of depressive and anxious symptoms during the COVID-19 pandemic, particularly for those who underwent an ICU stay. The ICU environment itself is inherently stressful, filled with the constant noise of various medical devices. Studies have provided strong evidence that the prolonged need for ventilation support and the loss of freedom of movement are key factors in the development of psychological problems among COVID-19 patients who had been treated in the ICU.

Key Words: COVID-19; Patient; Post-intensive care unit; Discharge; Mental health

Core Tip: A prolonged stay in the intensive care unit (ICU) for coronavirus disease 2019 can be psychologically traumatic to survivors. In addition to pandemic-related risk factors such as widespread contagion and lockdowns, it is crucial to emphasize the importance of monitoring the psychological health of individuals who have spent an extended period in the ICU.

Citation: Sarac E. Evaluation of the mental health of COVID-19 patients discharged from the intensive care unit. *World J Clin Cases* 2024; 12(33): 6587-6590
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6587.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6587

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak was declared a global public health emergency[1]. Despite ongoing efforts to combat the virus, it continues to spread in various forms. The clinical manifestations of COVID-19 vary widely, ranging from asymptomatic cases to severe physical and psychological issues, including multi-organ dysfunction[2-4]. Preventive measures such as social isolation, prolonged mask-wearing, and strict working conditions have had a significant impact on daily life. The disease poses a threat not only to physical health but also to mental well-being. Individuals in critical condition who were admitted to intensive care units (ICUs) face the highest risk of developing psychological distress later in life. Research supports the link between extended ICU stays, post-intensive care syndrome (PICS), and the onset of psychiatric disorders[5-8]. PICS can also lead to cognitive, physical, and mental health impairments.

In 5%-11% of cases, COVID-19 infection leads to medical complications that require a prolonged stay in an ICU with mechanical ventilation[5,9,10]. ICU hospitalization during COVID-19 treatment can be a traumatic experience. In addition to the many stressors associated with the pandemic, such as fear of the disease, social isolation, and uncertainty about the future, an extended ICU stay can further exacerbate a patient's psychological condition. Increasing evidence suggests that the virus has a significant emotional impact[2,11]. In particular, experiencing severe symptoms and requiring ICU admission may result in heightened anxiety, depression, and post-traumatic stress disorder (PTSD)[12,13].

Assessing the psychological health of COVID-19 survivors after ICU discharge is crucial for determining whether individuals receive appropriate mental health care during or after their ICU stay. Public health professionals have made significant efforts to prevent the spread of the disease and to minimize the comorbidities associated with COVID-19 treatments, including the psychological impact on survivors.

PICS

Critical illnesses are commonly associated with PICS, which affects many patients after ICU discharge. PICS is linked to high rates of psychological symptoms, including distress, anxiety, insomnia, and PTSD[14]. Preventative measures to reduce the incidence and severity of PICS are being implemented, such as orientation and communication strategies, early mobilization, and rehabilitation programs[15,16].

IMPORTANCE OF ASSESSING MENTAL HEALTH AMONG COVID-19 PATIENTS AFTER ICU DISCHARGE

To date, many studies exploring the impacts of the COVID-19 pandemic have focused primarily on physical or psychosocial outcomes. However, the literature is limited on the mental health of individuals who experienced severe symptoms and required ICU hospitalization. Previous research suggests that the long-term consequences of the virus include chronic fatigue and organ damage[17,18]. In addition to severe symptoms or physical disabilities, the pandemic has been associated with increased levels of anxiety, worry, and social avoidance behavior in the general population[19]. However, there is limited data on whether patients receive mental health care during or after their ICU admission[14,20]. It is well known that ICU admission can lead to various psychological disorders or negative emotions, including fear, nervousness, sadness, guilt, confusion, anger, numbness, and anxiety-induced insomnia[21-23]. Investigating the responses of COVID-19 survivors to their ICU hospitalization experience is crucial for providing better care and developing effective coping strategies.

There is strong evidence that preventive measures implemented during the pandemic, such as quarantine, isolation, and social distancing, may also contribute to the worsening of mental health in individuals and their family members[24,25].

Alhammad *et al*[26] published a significant study titled "Mental Health Status Among COVID-19 Patients Survivors of Critical Illness in Saudi Arabia: A 6-Month Follow-Up Questionnaire Study". This study focused on evaluating anxiety and depression in patients who had severe COVID-19. The research involved screening all patients with laboratory or radiological confirmation of COVID-19 who were either admitted to the ICU or under ICU observation for more than 24 h between April 2020 and November 2020. Data were collected using the Arabic version of the Hospital Anxiety and Depression Scale[27]. A total of 48 valid responses were received. The study concluded that individuals who were critically ill with the virus experienced anxiety or depression up to 6 months post-ICU discharge. These findings align with existing literature and confirm that the long-term impact of the disease persists even after discharge[28,29]. Piras *et al*[28] reported that patients commonly experienced negative feelings, anxiety, loneliness, and fear of dying. Another study

found that disabilities in daily activities and anxiety persisted up to 12 months after ICU discharge[30]. This evidence underscores the long-term mental health issues associated with extended ICU stays. The similarity in findings may be attributed to factors such as prolonged bed rest, the uncertainties associated with the virus, and the use of pharmacological sedation, which could lead to motor level impairments and nervous system deficits. Additionally, a study by Sun *et al*[31] found suggestive evidence of fear and stigma among individuals who experienced ICU admission. They also highlighted that the most challenging aspect was the feeling of complete isolation.

The results from studies indicate that the majority of individuals who experienced a prolonged ICU stay primarily faced mild to moderate levels of anxiety and depression related to their hospitalization. Given that long-term ICU stays can significantly impact patients' quality of life, it is crucial to identify those at risk to ensure effective management upon discharge and to provide continuity of care.

CLINICAL IMPLICATIONS

Since the onset of the COVID-19 pandemic, scientific research on psychological consequences has predominantly focused on objectively measurable aspects, such as panic disorder, insomnia, depression, and PTSD. However, there has been a neglect of the subjective experiences and emotions that may impact the mental health and quality of life of individuals who faced severe complications in the ICU.

CONCLUSION

The findings represent strong evidence that the prevalence of persistent psychological symptoms is higher among COVID-19 survivors following ICU hospitalization. Further research is suggested to identify individuals at risk for long-term effects of COVID-19 and to implement holistic care that begins before discharge and continues within the community after leaving the hospital or ICU.

ACKNOWLEDGEMENTS

I would like to thank the authors of the main study for their focus on evaluating anxiety and depression among patients with severe COVID-19. Their research has provided an important opportunity for me to comment on this critical issue.

FOOTNOTES

Author contributions: Sarac E performed the design and conceptualization of the study, investigation, obtainment of the resources, supervision, visualization of the data, and writing, review and editing of the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Country of origin: Türkiye

ORCID number: Elif Sarac 0000-0002-4126-9327.

S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Che XX

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World J Clin Cases 2024 November 26; 12(33): 6591-6594

DOI: 10.12998/wjcc.v12.i33.6591

ISSN 2307-8960 (online)

EDITORIAL

Advancements and challenges in gastrointestinal imaging

Eun Jeong Gong, Chang Seok Bang

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade C

P-Reviewer: Ohira K

Received: May 15, 2024
Revised: August 9, 2024
Accepted: August 16, 2024
Published online: November 26, 2024
Processing time: 134 Days and 22.5 Hours

Eun Jeong Gong, Department of Internal Medicine, Hallym University College of Medicine, Chun-cheon 24253, Gangwon-do, South Korea

Chang Seok Bang, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon Sacred Heart Hospital, Chuncheon 24253, Gangwon-do, South Korea

Corresponding author: Chang Seok Bang, MD, PhD, Associate Professor, Doctor, Research Scientist, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon Sacred Heart Hospital, Sakju-ro 77, Chuncheon 24253, Gangwon-do, South Korea. cloudslove@naver.com

Abstract

A recent review by Gulinac *et al*, provides an in-depth analysis of current clinical issues and challenges in gastrointestinal imaging. This editorial highlights the advancements in imaging techniques, including the integration of artificial intelligence and functional imaging modalities, and discusses the ongoing relevance of traditional nuclear medicine tests. The future of gastrointestinal imaging looks promising, with continuous improvements in resolution, enhanced ability to analyze color and texture beyond visual diagnosis, faster image processing, and the application of molecular imaging and nanoparticles expected to enhance diagnostic accuracy and clinical outcomes.

Key Words: Imaging methods; Gastrointestinal diseases; Gastrointestinal tract; Radiology; Tumors of the gastrointestinal tract

Core Tip: A recent review by Gulinac *et al*, provides an in-depth analysis of current clinical issues and challenges in gastrointestinal imaging. This editorial highlights the advancements in imaging techniques, including the integration of artificial intelligence and functional imaging modalities, and discusses the ongoing relevance of traditional nuclear medicine tests. The future of gastrointestinal imaging looks promising, with continuous improvements in resolution, enhanced ability to analyze color and texture beyond visual diagnosis, faster image processing, and the application of molecular imaging and nanoparticles expected to enhance diagnostic accuracy and clinical outcomes.

Citation: Gong EJ, Bang CS. Advancements and challenges in gastrointestinal imaging. *World J Clin Cases* 2024; 12(33): 6591-6594
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6591.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6591

INTRODUCTION

Imaging techniques are pivotal in modern gastroenterology, allowing for detailed examination and diagnosis of gastrointestinal diseases. A recent review by Gulinac *et al*[1], describes the current clinical issues and challenges in gastrointestinal imaging. This editorial highlights the key insights and implications of their findings.

EVOLUTION OF GASTROINTESTINAL IMAGING

Gulinac *et al*[1] provide a comprehensive overview of both non-invasive and invasive imaging modalities used in the evaluation of gastrointestinal diseases. Traditional methods such as plain X-ray, defecography, enterography, computed tomography (CT), or magnetic resonance imaging (MRI) remain foundational, particularly for assessing acute conditions like bowel perforation and obstruction. However, newer technologies like functional imaging or advanced CT/MRI techniques are revolutionizing the field.

KEY FINDINGS AND ADVANCES, CHALLENGES, AND LIMITATIONS

The review emphasizes several advancements and acknowledges the associated challenges. Videoendoscopy, including esophagogastroduodenoscopy and colonoscopy, remains a cornerstone for both diagnosis and therapeutic interventions of gastrointestinal luminal disorders. Image-enhanced endoscopy enhances visual diagnosis by allowing targeted biopsies and aiding in the decision-making process for endoscopic resection techniques. However, the effectiveness of these techniques is influenced by the experience and expertise of the endoscopists, with subjective interpretability and inter-observer variability tempering their widespread implementation[2,3]. Studies show that only experienced endoscopists with high confidence levels benefit significantly from this technology[4].

High-speed sequences and diffusion techniques in MRI, along with advanced CT imaging, provide detailed assessments of the gastrointestinal tract, aiding in the staging of cancers and evaluation of inflammatory diseases. Additionally, there is potential for advanced image processing to allow radiology to be a surrogate for biomarkers for certain gastrointestinal diseases[5]. Despite these advancements, high radiation exposure in CT, motion artifacts in MRI, and the invasive nature of endoscopy pose significant challenges. The effectiveness of imaging techniques heavily relies on the skill of the clinician, particularly in endoscopy and ultrasound. Furthermore, the high cost of advanced imaging technologies and the need for specialized training limit their widespread use.

ROLE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) is increasingly being integrated into gastrointestinal imaging to improve diagnostic accuracy and efficiency. Studies on computer-aided diagnosis (CAD) models in gastrointestinal endoscopy have shown that AI can augment clinical performance, reduce the burden on endoscopists from repetitive procedures, and facilitate concentration on professional activities[6,7]. CAD models provide consistent and robust answers, irrespective of the fatigue level of users, and can help in detecting hidden or hard-to-detect lesions. Additionally, they aid in the automated determination of the optimum classification and provide real-time clinical decision support systems, particularly beneficial for novice endoscopists[2,3]. AI and machine learning techniques hold the potential to overcome the limitations of visual diagnosis by providing more detailed analysis of image texture and color. However, current CAD models are often research-based and have limited practical application due to the unique characteristics of patients in different institutions[6,7]. The advancement of AI from traditional machine learning and deep learning to models with functionality, such as Transformers with self-attention, will likely enhance the clinical applicability of CAD models in the near future. Furthermore, the development of fusion techniques and ensemble models using diverse input imaging data could lead to the creation of more robust and accurate diagnostic methods. The ultimate goal of AI-enabled predictive models or imaging modalities should be to improve clinical patient outcomes; however, there are no studies or devices that have demonstrated this with high quality evidence.

FUNCTIONAL IMAGING MODALITIES

The review also discusses the importance of functional imaging modalities such as EndoFLIP (functional lumen imaging probe), which provides detailed assessments of the geometry and function of the gastrointestinal lumen. These tech-

niques are crucial for evaluating sphincter function and motility disorders, offering a less invasive alternative to traditional methods[1]. Contrast-enhanced ultrasound is another significant advancement, enhancing the visualization of vascularity and tissue perfusion in real-time. It is particularly useful in characterizing liver lesions and assessing inflammatory bowel diseases, providing a non-invasive method to gather functional and anatomical information simultaneously[1]. High-resolution electrogastrography is an emerging technique that records electrical activity of the stomach with improved spatial resolution, allowing for a more detailed analysis of gastric motility and function. This can help in diagnosing motility disorders such as gastroparesis and functional dyspepsia, providing a non-invasive method to assess gastric electrical activity[1]. High-resolution manometry (HRM) is another advanced diagnostic tool that measures intraluminal pressure within the gastrointestinal tract with high spatial and temporal resolution. HRM is particularly useful for diagnosing esophageal motility disorders and evaluating esophageal function, offering detailed pressure topography that aids in the identification of specific motility abnormalities. HRM in anorectal disorders also provides physiological insights to the physicians for the differentiation of defecatory disorders[1]. The wireless motility capsule is an emerging technology that offers a non-invasive method to assess gastrointestinal motility throughout the entire gastrointestinal tract. This small, ingestible device measures pressure, pH, and temperature as it travels through the gastrointestinal system, providing valuable data on gastric emptying, small bowel transit, and colonic transit times. The wireless motility capsule can help diagnose conditions like gastroparesis, chronic constipation, and other motility disorders, offering an alternative to more invasive procedures like manometry.

NUCLEAR MEDICINE IN GASTROINTESTINAL IMAGING

Traditional nuclear medicine tests like the gastric emptying test or DISIDA scan continue to be valuable tools in gastrointestinal imaging. These tests provide unique insights into gastric motility and biliary function that are not easily replicated by other imaging modalities. Additionally, intestinal transit scintigraphy is used to evaluate small and large bowel transit times, helping to diagnose conditions such as chronic constipation and motility disorders. Gastrointestinal bleeding scintigraphy is another crucial tool, enabling the detection and localization of active gastrointestinal bleeding, which is especially useful in patients with obscure or intermittent bleeding when other diagnostic methods fail. Despite advances in imaging technology, there remains a lack of suitable alternatives to these nuclear medicine tests for certain diagnostic purposes.

EMERGING AND ADVANCED IMAGING TECHNIQUES

New modalities such as MR defecography and CT/MR enterography are providing more comprehensive views of gastrointestinal structures and functions. MR defecography allows detailed imaging of the pelvic floor and anorectal region during defecation, which is invaluable in diagnosing defecatory disorders. CT/MR enterography offers enhanced visualization of the small intestine, helping in the diagnosis and management of inflammatory bowel diseases like Crohn's disease. Confocal laser endomicroscopy after the injection of fluorescently labeled antibodies shows great potential for providing real-time, high-resolution histological images, allowing for precise characterization of lesions. These advanced imaging techniques represent significant strides in the field and have the potential to improve diagnostic accuracy and patient outcomes[8]. Elastography is a noninvasive test used to check the stiffness of the organs and it is mostly used to evaluate liver fibrosis. This also can be done using the endoscopic ultrasound based method[9].

THE FUTURE OF GASTROINTESTINAL IMAGING

Gulinac *et al*[1] suggest that the future of gastrointestinal imaging lies in the integration of multimodal approaches and the development of new sub-modalities. The trend towards faster image acquisition, higher resolution, and enhanced software for post-processing is expected to continue. Additionally, molecular imaging and the use of nanoparticles as contrast agents hold promise for more precise and early diagnosis of gastrointestinal diseases. The development of fusion techniques and ensemble AI models using various input imaging data could further enhance the diagnostic capabilities, leading to innovative diagnostic methods.

CONCLUSION

While there are significant challenges, the ongoing technological advancements offer a promising future. The integration of various imaging modalities, the incorporation of AI, and the continuous improvement in imaging techniques will undoubtedly enhance the field of gastroenterology, leading to better patient outcomes and more efficient clinical practices. Advances such as higher resolution, enhanced analysis of color and texture beyond visual diagnosis, faster image processing, and the application of molecular imaging and nanoparticles are expected to drive the future of gastrointestinal imaging. Despite these advancements, traditional nuclear medicine tests remain indispensable, highlighting the need for a balanced approach that leverages both new and established technologies.

FOOTNOTES

Author contributions: Gong EJ and Bang CS contributed to conceptualization; Gong EJ and Bang CS contributed to methodology; Gong EJ and Bang CS contributed to investigation; Gong EJ and Bang CS wrote the original draft; Bang CS reviewed and edited the draft; Bang CS contributed to supervision; and all authors have read and agreed to the published version of the manuscript.

Supported by the Bio&Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT), No. RS-2023-00223501.

Conflict-of-interest statement: All authors declare no conflict of interest for this article.

Country of origin: South Korea

ORCID number: Eun Jeong Gong 0000-0003-3996-3472; Chang Seok Bang 0000-0003-4908-5431.

S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Xu ZH

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6595-6603

DOI: 10.12998/wjcc.v12.i33.6595

ISSN 2307-8960 (online)

EDITORIAL

Prothrombotic state and thrombotic events in COVID-19 pandemic period, including portal vein and splenic artery thromboses

Ozgur Karcioglu, Canan Akman, Göksu Afacan Ozturk

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Cheng TH

Received: May 26, 2024

Revised: August 2, 2024

Accepted: August 23, 2024

Published online: November 26, 2024

Processing time: 123 Days and 8.8 Hours

Ozgur Karcioglu, Department of Emergency Medicine, University of Health Sciences, Istanbul Education and Research Hospital, Istanbul 34140, Bakırkoy, Türkiye

Canan Akman, Department of Emergency Medicine, Canakkale Onsekiz Mart University, Canakkale 17000, Çanakkale, Türkiye

Göksu Afacan Ozturk, Department of Emergency Medicine, Istanbul Aydin University, Istanbul 34295, Kucukcekmece, Istanbul, Türkiye

Co-first authors: Ozgur Karcioglu and Canan Akman.

Corresponding author: Ozgur Karcioglu, MD, Academic Research, Full Professor, Senior Researcher, Department of Emergency Medicine, University of Health Sciences, Istanbul Education and Research Hospital, Fatih, Istanbul 34140, Bakırkoy, Türkiye.
okarcioglu@gmail.com

Abstract

This editorial article is intended to perform a discussion on the manuscript entitled "Simultaneous portal vein thrombosis and splenic vein thrombosis in a COVID-19 patient: A case report and review of literature" written by Abramowitz *et al*. The article focuses on the diagnostic processes in a 77-year-old-male patient with a simultaneous portal vein and splenic artery thrombosis accompanying coronavirus disease 2019 (COVID-19). The authors postulated that splanchnic thrombosis should be on the list of differential diagnoses in a patient presenting with abdominal pain in presence of a COVID-19 infection. The tendency for venous and arterial thrombosis in COVID-19 patients is encountered, largely attributed to hypercoagulopathy. In general, venous thromboembolism mostly manifest as deep vein thrombosis (DVT), pulmonary embolism (PE) or catheter-related thromboembolic events. Acute PE, DVT, cerebrovascular events and myocardial infarction are seen as the most common thromboembolic complications in COVID-19 patients. COVID-19-associated hemostatic abnormalities include mild thrombocytopenia and increased D-dimer level. Similar to other coagulopathies, the treatment of the underlying condition is the mainstay. Addition of antiplatelet agents can be considered in critically ill patients at low bleeding risk, not on therapeutic anticoagulation, and receiving gastric acid suppression Early administration of antithrombotic drugs will have a beneficial effect in both the prevention and treatment of thrombotic events, especially in non-ambulatory patients. Low molecular weight heparin (LMWH) should be started if there is no contraindication, including in non-critical patients who are at

risk of hospitalization LMWH (enoxaparin) is preferred to standard heparin.

Key Words: Prothrombotic state; Thrombotic events; COVID-19; Pandemic; Thromboembolism

Core Tip: Venous thromboembolisms constitute a common complication of coronavirus disease 2019 (COVID-19) and mostly manifest as deep venous thromboses, pulmonary embolism, myocardial infarction or catheter-related thromboembolic events. On the other hand, portal vein and splenic artery thromboses are rarely encountered. Since the portal vein forms the confluence of the splenic and superior mesenteric veins, portal vein thrombosis may extend to the splenic or superior mesenteric veins. Prophylactic dose anticoagulation is associated with favorable efficacy and safety in those with COVID-19, including portal vein and splenic artery thromboses.

Citation: Karcioglu O, Akman C, Ozturk GA. Prothrombotic state and thrombotic events in COVID-19 pandemic period, including portal vein and splenic artery thromboses. *World J Clin Cases* 2024; 12(33): 6595-6603
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6595.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6595

INTRODUCTION

This editorial article is intended to perform a discussion on the manuscript entitled "Simultaneous portal vein thrombosis and splenic vein thrombosis in a COVID-19 patient: A case report and review of literature" written by Abramowitz *et al* [1]. The article focuses on the diagnostic processes in a 77-year-old-male patient with a simultaneous portal vein and splenic artery thrombosis accompanying coronavirus disease 2019 (COVID-19). The authors also pointed out that numerous disorders involving coagulation system can trigger such unusual thrombotic manifestations which are mostly attributed to hypercoagulable states. Emergent abdominal imaging has been emphasized to detect and treat thrombus and related problems expediently. They postulated that splanchnic thrombosis should be on the list of differential diagnoses in a patient presenting with abdominal pain in presence of a COVID-19 infection.

COVID-19 has caused serious illness and death all over the world. Although the illness primarily causes serious respiratory diseases, there is an increased risk of thromboembolic events. Patients with COVID-19 are increasingly being recognized as being at risk of developing prothrombotic complications such as acute mesenteric ischemia and portal vein thrombosis (PVT). Both bleeding and thrombosis can result in significant morbidity in COVID-19. The entity paves the way to arterial thromboembolic events (*i.e.*, stroke and/or extremity ischemia) as well as small vessel thrombosis, which are frequently encountered at autopsy in the pulmonary vessels.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affected the world population *via* a global pandemic, and many people lost their lives. COVID-19 is a disease that begins with symptoms of fever, cough, and shortness of breath, and progresses to a severe infection in which systemic inflammatory response (Systemic Inflammatory Response Syndrome), acute respiratory disease syndrome, and multiple organ failure ensue with a high rate of death and disability [2].

Thrombotic events are triggered by COVID-19 infection *via* various mechanisms including platelet activation, activation of the coagulation cascade, the formation of neutrophil extracellular traps (NETs) and inflammaton pathways also known as "cytokine storm"[3]. NETs are described as a web-like material structured from DNA and various proteins resulting in a pathological process called "NETosis"[4]. These structures have pro-inflammatory properties, interfering in the pathogenesis of inflammatory processes, including atherogenesis, arterial and venous thrombosis[5]. NETs enhance the production of cytokines, as well as the pro-coagulant and pro-thrombotic status[6,7]. Cytokine storm activate the coagulation cascade, while coagulation factors can act as triggers of the cytokine storm[8-10]. The development of thrombi which plays critical role in the pathogenesis of multi-organ injury follows overproduction of inflammatory cytokines[9,10]. Figure 1 illustrates the pathological and prothrombotic mechanisms of the COVID-19 infection.

Coagulopathy and disseminated intravascular coagulation (DIC) are the most important causes of mortality in COVID-19 patients. Research showed that the risk of venous and arterial thromboembolism is associated with coagulation disorders. Patients are generally prone to excessive inflammation, embolization, hypoxia, DIC, and both venous and arterial thromboembolic events. COVID-19-associated coagulopathy affects many organs, including the lungs, brain, heart and extremities. Development of thrombi, especially in small pulmonary vessels, causes acute severe acute respiratory syndrome, resulting in death. Of note, there are studies which reported a low risk of venous and arterial thrombi in ambulatory and post-discharge COVID-19 patients, with a higher risk in post-discharge patients compared with ambulatory patients [11].

Acute pulmonary embolism (PE), deep vein thrombosis (DVT), cerebrovascular events and myocardial infarction (MI) are seen as the most common thromboembolic complications in COVID-19 patients[12,13]. Acute mesenteric ischemia is a life-threatening abdominal emergency accompanied by poor clinical outcomes[14]. Bowel wall abnormalities were detected in around one-third of abdominal computed tomography images, including pneumatosis and portal venous gas.

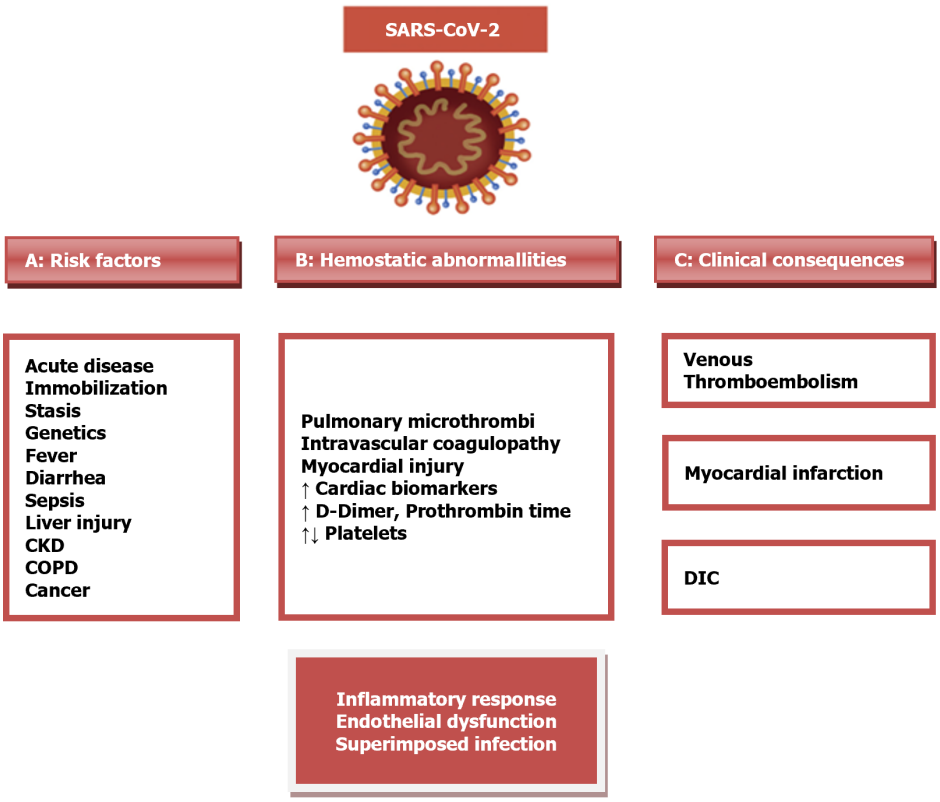

Figure 1 Schematisation of the pathological and prothrombotic mechanisms and pathways of the severe acute respiratory syndrome coronavirus 2 infection. A: Severe acute respiratory syndrome coronavirus 2 infection leads to endothelial and hemostatic activation with the release of inflammatory mediators, increase of Von Willebrand factor and tissue factor. Patients with severe infection has more remarkable inflammatory response, lymphopenia and thrombocytopenia. Liver injury, impaired coagulation and decreased antithrombin formation are observed; B: Coronavirus disease 2019 is known to trigger hemostatic irregularity and release of cardiac troponins into bloodstream; C: Disseminated intravascular coagulation is observed in cases of increased prothrombotic state, venous thromboembolism, myocardial infarction, hemostatic irregularity. CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; DIC: Disseminated intravascular coagulation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Intestinal ischemia was diagnosed in some of these patients, which was attributed to thrombotic diseases of small vessels [15].

Cytokine storm and endothelial dysfunction ensued in the course of COVID-19 have been accused of causing significant venous thromboembolisms (VTE). Increased levels of D-dimer and fibrin degradation products are linked to high rates of adverse consequences[16]. Of note, COVID-19 patients have also increased levels of lupus anticoagulants. The macrophage activation syndrome, the complement cascade, and the renin-angiotensin system are also blamed in these pathophysiological mechanisms[17].

Pro-inflammatory cytokine release is associated with endothelial dysfunction and activation of coagulation pathways, which is reflected by elevated D-dimer levels and impaired coagulation markers. Thrombosis result in tissue ischemia combined with endothelial damage which lead to microthrombi, macrothrombi and thromboembolic events. If thrombosis develops in different organ systems as a result of excessive immune activation, multiorgan failure may ensue.

PVT is known to encompass blockade of the portal vein by a thrombus. Thrombosis can develop in the main body of the portal vein or its intrahepatic branches[18]. Since the portal vein forms the confluence of the splenic and superior mesenteric veins, PVT may extend to the splenic or superior mesenteric veins. In most cases, the entity is associated with liver failure, although it can ensue without a liver disease like malignancy, abdominal sepsis, or pancreatitis. PVT occurs in two groups of patients: Those with chronic hepatic failure and patients with prothrombotic disorders. The liver functions are mostly around expected levels in the latter group. complication of PVT include portal hypertension, ischemic bowel disease, septic PVT, and portal cholangiopathy[18,19].

In those with PVT, anticoagulation is necessary in case of impending intestinal ischemia, hepatic failure awaiting liver transplantation, and a compensated liver disease with a new diagnosis of acute PVT or PVT with asymptomatic mesenteric venous occlusion. Enoxaparin is preferable, which has not any important side effects or hemorrhagic events in cirrhotic patients.

SARS-CoV-2 is a single-stranded RNA coronavirus. It enters human cells by binding to ACE-2, which is activated mainly in lung alveoli, cardiac myocytes, vascular endothelium and other cells[2,20,21]. Depending on the type of surface, the virus can survive for up to 24-72 hours and paves the way for the transmission of infections[22]. Some mechanisms of coagulopathy that may predispose to thrombotic events are given below.

During the process of DIC, hyper-coagulopathy occurs as a result of endothelial cell dysfunction, overproduction of thrombin, and inhibition of fibrinolysis.

MARKERS OF COVID-19, HEMOSTASIS, MYOCARDIAL INJURY AND THROMBOTIC DISEASE

COVID-19-associated hemostatic abnormalities include mild thrombocytopenia and increased D-dimer level. These parameters are concurrent with the increased risk of mechanical ventilation, intensive care unit (ICU) admission, and death[23,24]. D-dimer elevation more than 2 times constitutes a risk factor for VTE. It is recommended that anticoagulant prophylaxis last more than 45 days. The severity of the disease is related to prothrombin time (PT), international normalized ratio (INR) prolongation, thrombin time prolongation, and active partial thromboplastin time test (aPTT) shortening (Figure 2)[2,25-27].

High troponin level has been associated with poor outcome in COVID-19. Nonspecific myocardial ischemia includes troponin elevation due to renal dysfunction, myocarditis, PE, and MI. It is important to consider the clinical picture in the evaluation of thrombotic events such as PE[28,29].

Ultrasonography, echocardiography (ECHO), pulmonary angiography and tomography can be used to evaluate cardiopulmonary and circulatory thrombotic events. Right ventricular dysfunction is valuable for PE. Right ventricular functions, wall motions, and clot can be examined in ECHO[30].

CLINICAL CHARACTERISTICS AND COURSE

The tendency for venous and arterial thrombosis in COVID-19 patients is encountered, largely attributed to hypercoagulopathy. In general, VTEs mostly manifest as DVTs, PE or catheter-related thromboembolic events. Thrombosis can occur in various sites, including the deep veins of the lower extremity (femoral, iliac, and popliteal veins), upper extremity, veins and more rarely, the superior vena cava, jugular vein, cerebral venous sinus, cavernous sinus, and retinal vein[17].

COVID-19 paves the way for thromboembolic complications even in the post-treatment period. It has been observed that the increased risk of VTE in patients with COVID-19 continues for a longer period of time (around two months). Pharmacological prophylaxis of VTE is recommended if the patient is elderly, has comorbid diseases (obesity, cardiovascular disease, hypertension, diabetes), has a history of VTE, and is hospitalized in the ICU, unless there are contraindications.

Due to the risk of severe thromboinflammation, and consequent DIC, anticoagulation in prophylactic dose is associated with favorable efficacy and safety in COVID-19 patients. A recent Cochrane analysis revealed that prophylactic anticoagulants may result in little or no difference in risk of VTE, hospitalisation, or adverse events when compared with antiplatelet agents (low-certainty evidence)[31]. Authors emphasized that for there were only short-term data from one study, these results should be interpreted with caution.

Low molecular weight heparins (LMWH) are preferred treatments over parenteral anticoagulation [unfractionated heparin (UFH)] due to need for frequent blood tests to monitor the achievement of therapeutic levels of aPTT. Advantages of direct oral anticoagulants (DOAC) include no need for monitoring, easy discharge planning, and outpatient management. In brief, LMWH and DOACs are the preferred agents[30]. Late cardiovascular events and all-cause mortality were high in the year following hospitalization for COVID-19. A retrospective follow-up study reported that administration of prophylactic DOAC or dipyridamole in the early post-discharge period improved long-term (393 ± 87 days) cardiovascular outcomes and all-cause mortality in patients with COVID-19[32].

Coronary artery and vascular diseases

High troponin levels and MI are observed due to the increased risk of thrombosis due to pathogenesis of COVID-19 pneumonia. The importance of risk classification (very high, high, moderate, low) in non-ST-elevation MI is given in the European Cardiology Heart Society COVID-19 guideline[33]. If the patient does not have elevated troponin levels and is clinically stable [*i.e.*, no electrocardiogram (ECG) changes, no chest discomfort], conservative treatment is recommended, whereas invasive intervention is among the recommendations in the high-risk group, should complaints continue despite medical treatment. Considering the time to obtain a COVID test and its result will take long, all patients are considered to be COVID-19 (+) in ST-elevation MI (STEMI), the diagnosis-reperfusion time should not exceed 120 minutes. Thrombolytic therapy should be considered in centers where there is no coronary catheterization laboratory[30].

There is scarce data regarding acute limb ischemia (ALI) as a complication related to thrombogenesis. A study conducted in Italy stated that ALI incidences increased during the COVID-19 pandemic period. While most of the ALI occurs in the lower extremity, it is also seen in the upper extremity. Amputation has been needed in these cases despite anticoagulant treatment[34-36].

A 6% increase in the incidence of acute ischemic stroke has been reported in those with COVID-19 infection. In addition to advanced age and comorbid diseases, the progression of acute severe respiratory failure, multiple organ failure, coagulopathy, DIC or cardiac involvement are blamed for this situation and for the increased risk of stroke. It should be noted that the SARS-CoV-2 virus is known to be an agent with neurotropic potential. Authors of multicenter studies indicated that severity of COVID-19 is associated with an increased risk of acute stroke[37]. There is a potential for both hemorrhagic and ischemic stroke due to coagulopathy.

As the clinical severity of the COVID-19 infection increases, the symptoms of the neurological condition worsen as well. In case of doubt, diffusion magnetic resonance imaging should be elicited. Recombinant tissue-type plasminogen activator should be administered intravenously if the indication for administration is verified.

COVID-19 may pave the way for the DIC, which leads to a high death toll. Supportive care, addressing the underlying hypoxic condition, and evaluation for co-infection are important. Diagnosis can be established by calculating the score

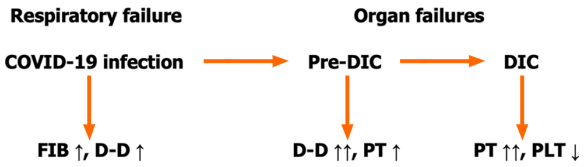

Figure 2 Coagulopathy in coronavirus disease 2019 patients. D-D: D-dimer; DIC: Disseminated intravascular coagulation; FIB: Fibrinogen; PLT: Platelet; PT: Prothrombin time; COVID-19: Coronavirus disease 2019.

from the guide of the International Society on Thrombosis and Haemostasis (ISTH; Table 1)[38].

Bacterial superinfections should be treated aggressively. LMWHs prevent VTE and can change the course of DIC by reducing thrombin formation. Long-term antiplatelet therapy should often be discontinued in DIC patients unless agents are definitely required (recent acute coronary syndrome or stent implantation). Antiplatelet therapy should be individualized in DIC patients. Healing process in DIC depends on endogenous fibrinolysis, which breaks down the thrombus. Blood product support should be considered based on septic coagulopathy occurring in bleeding in DIC in those with COVID-19. In patients with DIC, it is recommended to administer platelet suspension when the platelet count is < 50 × 10^9/L, PT/PTT prolongation, fresh frozen plasma if INR > 1.8, and fibrinogen concentrate or cryoprecipitate when the fibrinogen level is < 1.5 g/L.

MANAGEMENT

Similar to other coagulopathies, the treatment of the underlying condition is the mainstay. In patients with COVID-19 infection, coagulopathy occurs on approximately day 7. Markers indicating coagulopathy (platelet, PT, aPTT, fibrinogen, D-dimer) should be monitored. The American Society of Chest Physicians recommends that patients who developed VTE in the setting of COVID-19 should be anticoagulated for 3 to 6 months[39].

LMWH should be started if there is no contraindication, including in non-critical patients who are at risk of hospitalization. The recommended treatment for prophylaxis is LMWH (enoxaparin) that is preferred to standard heparin. LMWH causes thrombocytopenia less frequently. Oral anticoagulants are not routinely recommended for prophylaxis. LMWHs can be administered intravenously or subcutaneously. When evaluated in terms of drug interactions, they have a lower side effect potential than oral anticoagulants. LMWHs have shorter half-lives[30]. The use of fondaparinux is recommended in case of heparin-induced thrombocytopenia.

Should the patient be admitted to hospital due to an acute thrombotic event in the setting of COVID-19, the use of heparins (LMWH or UFH) should be preferred over a DOAC, with weight-based therapeutic-dose LMWH at twice daily dosing as the preferred agent. For obese patients, the use of weight-adjusted LMWH is recommended. For patients on IV UFH, weight-adjusted and nomogram-based monitoring with anti-Xa levels should be preferred over APTT monitoring [40].

A novel predictive model based on one dimensional convolutional neural networks (1D CNN) was designed to use clinical variables in predicting the survival outcome of COVID-19 patients. The authors of this 1D CNN disclosed that heparin treatment significantly influenced the survival outcome[41].

ISTH COVID-19 Antithrombotic Guidelines do not recommend antiplatelet therapy added routinely in critically ill COVID-19 patients[38]. Nonetheless, addition of antiplatelet agents can be considered in critically ill patients at low bleeding risk, not on therapeutic anticoagulation, and receiving gastric acid suppression[40]. This regimen may include low-dose aspirin or a P2Y12 inhibitor besides standard low-dose heparin prophylaxis, unless the patient has to receive therapeutic anticoagulation. Low-dose aspirin, clopidogrel and other P2Y12 inhibitors were compared with each other in the REMAP-CAP study in critically ill COVID-19 patients as add-on therapies and disclosed no benefit in improving survival. On the other hand, a significant improvement was reported in the secondary outcome of all-cause mortality until discharge[42].

Dipyridamole

Dipyridamole has been approved for use to prevent stroke, among other indications as an antiplatelet drug, which may help improve the clinical outcomes of COVID-19 treatment[43]. Dipyridamole has been suggested to have beneficial effects in the treatment of NETs-evoked digital ischemia[44]. It is generally safe, affordable, and available worldwide. 75 mg twice a day oral administration can be used for its antiplatelet and anti-inflammatory effects, as it reduces the replication of the SARS-CoV-2 virus and antiviral load, in the early stages of the disease / inflammation period. Research disclosed that it is recommended for the first 14 days and may cause hypotension.

Aspirin

All intracellular thrombotic pathways which are essential for viral replication, and resultant inflammatory responses, hypercoagulability, and platelet activation are affected by aspirin treatment. In this way, aspirin is a useful adjunctive treatment of COVID-19. Moreover, Tantry *et al*[45] cited that inhaled formulation with its rapid effects may enhance direct delivery to the lung, which is the key organ damaged in COVID-19 during the critical initial course of the disease, whereas the 150-325 mg/day can be used for long-term treatment to prevent thrombotic event occurrences.

Table 1 International Society on Thrombosis and Haemostasis criteria (> 5 points is indicative of disseminated intravascular coagulation)

Variable	Values	Points
Platelets (× 10^9/L)	> 100	0
	50-100	1
	< 50	2
D-dimer/fibrin degradation products	None	0
	Moderate increase	2
	Severe increase	3
PT	< 3 seconds	0
	3-6 seconds	1
	> 6 seconds	2
Fibrinogen (g/L)	> 1	0
	< 1	1

PT: Prothrombin time.

Administration of 100 mg aspirin in COVID-19 patients reduces the lung-damaging effect of the disease, but there is scarcity of research data. There are reports that patients with multisystem inflammatory syndrome in children (MIS-C) and cardiac involvement associated with COVID-19 benefited from aspirin treatment[46,47]. Medical management of MIS-C and cardiac sequelae have included supportive care, intravenous immunoglobulins, and corticosteroids, as well as immunomodulators, monoclonal antibodies, aspirin, and therapeutic anticoagulation, which have prevented serious outcomes in the majority of pediatric patients[48]. In a cohort study of adult patients with COVID-19, aspirin use at least 7 days before hospitalization or within 24 hours of hospitalization was associated with lower rates of mechanical ventilation (36% *vs* 48%) and ICU admission (39% *vs* 51%)[49].

Thrombolytic therapy

It is given in cases of STEMI on ECG, acute ischemic stroke, and massive PE leading to hemodynamic compromise (systolic blood pressure < 90 mmHg or obstructive shock findings).

Mechanical prophylaxis

In cases where pharmacological prophylaxis is not appropriate, intermittent pneumatic compression devices or compression stockings can be used. It can also be applied as an adjunct to treatment in patients with limited mobility[30].

CONCLUSION

COVID-19 infection can lead to serious conditions. Growing awareness of the medical community on the prothrombotic effect in COVID-19 stimulates more comprehensive diagnostic studies for thrombotic complications. Early administration of antithrombotic drugs will have a beneficial effect in both the prevention and treatment of thrombotic events, especially in non-ambulatory patients. Prophylactic dose anticoagulation is associated with good efficacy and safety in those with COVID-19, including portal vein and splenic artery thromboses.

FOOTNOTES

Author contributions: Karcioglu O and Akman C contribute equally to this study as co-first authors. Karcioglu O, Akman C, and Ozturk GA designed the research study; Karcioglu O, Akman C, and Ozturk GA contributed to original draft preparation, and data curation; Karcioglu O, Akman C, and Ozturk GA analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: Author(s) certify that there is no conflict of interest related to the manuscript. If any potential conflict-of-interest exists, author(s) certify that it is fully disclosed.

Country of origin: Türkiye

ORCID number: Ozgur Karcioglu 0000-0002-8814-6164; Canan Akman 0000-0002-3427-5649; Göksu Afacan Ozturk 0000-0002-2755-2660.

S-Editor: Lin C
L-Editor: A
P-Editor: Chen YX

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World J Clin Cases 2024 November 26; 12(33): 6604-6607

DOI: 10.12998/wjcc.v12.i33.6604

ISSN 2307-8960 (online)

EDITORIAL

Early screening to identify and diagnose primary nasal tuberculosis in patients with tumor necrosis factor inhibitors

Dan-Xiang Shen, Yu-Wei Wang, Zhi-Min Lin, Di Jin, Zhen-Hua Ying, Chen Li

Specialty type: Otorhinolaryngology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade A

Creativity or Innovation: Grade A

Scientific Significance: Grade A

P-Reviewer: Gravina AG

Received: June 4, 2024

Revised: September 17, 2024

Accepted: September 23, 2024

Published online: November 26, 2024

Processing time: 114 Days and 19.2 Hours

Dan-Xiang Shen, Department of Internal Medicine, Changxing Third People's Hospital, Huzhou 313000, Zhejiang Province, China

Dan-Xiang Shen, Zhen-Hua Ying, Department of Rheumatology and Immunology, Jinzhou Medical University Graduate Training Base Zhejiang Provincial People's Hospital, Center for General Practice Medicine, Zhejiang Provincial People's Hospital, Hangzhou 310000, Zhejiang Province, China

Dan-Xiang Shen, Zhen-Hua Ying, Department of Rheumatology, Zhejiang Provincial Key Laboratory of Traditional Chinese Medicine Cultivation for Arthritis Diagnosis and Treatment, Hangzhou 310000, Zhejiang Province, China

Yu-Wei Wang, Department of Cardiology, Yidu Central Hospital of Weifang, Weifang 261000, Shandong Province, China

Zhi-Min Lin, Third Affiliated Hospital, Beijing University of Chinese Medicine, Beijing 100020, China

Di Jin, Department of Rheumatology, Weifang People's Hospital, Weifang 261000, Shandong Province, China

Chen Li, Department of Rheumatology, Fangshan Hospital, Beijing University of Chinese Medicine, Beijing 102400, China

Co-first authors: Dan-Xiang Shen and Yu-Wei Wang.

Co-corresponding authors: Zhen-Hua Ying and Chen Li.

Corresponding author: Chen Li, MD, Chief Doctor, Doctor, Staff Physician, Department of Rheumatology, Fangshan Hospital, Beijing University of Chinese Medicine, No. 151 Chengguan South Street, Fangshan District, Beijing 102400, China. casio1981@163.com

Abstract

In this editorial, we comment on the article by Liu *et al*. Based on our analysis of a case report, we consider that early screening and recognition of primary nasal tuberculosis are crucial for patients undergoing treatment with tumor necrosis factor inhibitor (TNFi). While TNFi therapy increases the risk of reactivating latent tuberculosis, primary nasal tuberculosis remains rare due to the protective mechanisms of the nasal mucosa. Risk factors for primary nasal tuberculosis include minimally invasive nasal surgery, diabetes, and human immunodefi-

ciency virus. Patients with early symptoms such as nasal congestion, rhinorrhea, altered olfaction, epistaxis, or ulceration, and unresponsive to conventional antibiotics and antihistamines should undergo early rhinoscopy, possibly followed by repeated tissue biopsies and acid-fast bacilli culture when necessary. When diagnosis is challenging, it is essential to consider local tuberculosis epidemiology and the efficacy of diagnostic anti-tuberculosis treatment. The preferred method for tuberculosis screening is the Interferon Gamma Release Assay, with a general recommendation for screening at 3 and 6 months after initial treatment and then every six months. However, the optimal frequency is not yet consensus-driven and may be increased in economically viable settings.

Key Words: Tumor necrosis factor inhibitor; Interferon-gamma release assay; Primary nasal tuberculosis; Rhinoscopy; Diabetes mellitus

Core Tip: Patients receiving tumor necrosis factor inhibitor therapy rarely develop primary nasal tuberculosis, with diabetes, human immunodeficiency virus, and minimally invasive nasal surgery being risk factors. Early nasal endoscopy and an appropriately increased frequency of interferon gamma release assay testing may aid in the early screening and identification of nasal tuberculosis.

Citation: Shen DX, Wang YW, Lin ZM, Jin D, Ying ZH, Li C. Early screening to identify and diagnose primary nasal tuberculosis in patients with tumor necrosis factor inhibitors. *World J Clin Cases* 2024; 12(33): 6604-6607
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6604.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6604

INTRODUCTION

Tumor necrosis factor inhibitors (TNFi) have promising efficacy in refractory inflammatory bowel disease, rheumatoid arthritis, psoriasis, and ankylosing spondylitis, but inevitably have some adverse effects. Before starting TNFi therapy, infectious diseases, such as coronavirus disease 2019 (COVID-19), human immunodeficiency virus (HIV), hepatitis, and tuberculosis, are generally screened. Patients with psoriasis or inflammatory bowel disease undergoing TNFi treatment are not at an increased risk of developing severe COVID-19[1], and overall, COVID-19 vaccination is considered safe[2]. Notably, tumour necrosis factor alpha is an important cytokine for macrophage activation and is essential for host control of *Mycobacterium tuberculosis* (Mtb). However, TNFi can cause latent tuberculosis (TB) reactivation with an approximate 2–8-fold risk[3], and the incidence of TB is 3–4-fold higher with adalimumab and infliximab than with etanercept[4]. Most cases are extrapulmonary tuberculosis; primary nasal TB is rare. This condition is related to the protective mechanisms of the nasal mucosa, including ciliary clearance, bactericidal activity of nasal secretions, mechanical filtration by nasal hairs, and intrinsic resistance to mycobacterial infections[5], leading to a delayed diagnosis or misdiagnosis. For patients with latent tuberculosis infection (LTBI) who require TNFi, prophylactic anti-TB treatment is administered first.

IDENTIFICATION AND DIAGNOSIS OF PRIMARY NASAL TB

Liu *et al*[6] reported the case of a 58-year-old man who presented with right-sided nasal congestion and bloody discharge for one month, with a medical history of psoriasis, three years of adalimumab therapy, and right-sided functional endoscopic sinus surgery. The patient was diagnosed with primary nasal TB due to seroconversion in the 3rd year of adalimumab treatment; thickening, inflammation, and crusting changes in the nasal mucosa seen on nasal endoscopy; chronic granulomatous changes seen on repeat biopsy of the lesion; and antacid bacilli detected by Ziehl-Neelsen staining. The lesion improved after anti-TB treatment was administered. This case reminds clinicians to be vigilant for the development of nasal TB when early nonspecific nasopharyngeal symptoms develop in patients using TNFi, and that regular screening can avoid delayed diagnosis. The current frequency of LTBI screening in patients with psoriasis treated with TNFi should be based on medical history, risk of exposure, tuberculin skin testing (TST), and interferon gamma release assay (IGRA) results[7], generally once every six months[8]. However, the study did not state the frequency of T-SPOT TB tests, which could potentially delay the diagnosis of TB.

Primary nasal TB is more prevalent in females[7], and it is considered rare due to the protective mechanism of the nasal mucosa. To date, only two cases of primary nasal TB in patients treated with TNFi have been reported. Patients with primary nasal TB present with symptoms such as nasal congestion, nasal discharge, altered sense of smell, epistaxis, and ulceration; primarily unilateral[9] and conventional antibiotic and antihistamine therapy is ineffective. Early refinement of endoscopy is recommended as it can reveal sessile masses, crusts, scarring, and adhesions at the nasal septum and turbinates. In later stages, ulceration, septal perforation, and involvement of the sinuses and orbits may occur. A pathological biopsy of the nasal mass is necessary to visualize granulomatous inflammation, some of which lacks caseous

Table 1 Key characteristics of primary nasal tuberculosis induced by tumor necrosis factor inhibitor

Symptoms	Risk factors	Epidemiology	Types of TNFi	Treatment	IGRA	Nasal biopsy	Tissue culture
Nasal congestion; Rhinorrhea; altered olfaction; Epistaxis; Ulcers, *etc.*	Diabetes; HIV; Minimally invasive nasal surgery	High tuberculosis prevalence areas	Adalimumab and infliximab increase TB risk 3-4 times more than etanercept	Ineffective conventional antibiotics and antihistamines; diagnostic anti-tuberculosis effective	Negative to positive	Granulomatous inflammation with or without caseous changes	Positive for Mtb

TNFi: Tumor necrosis factor inhibitor; HIV: Human immunodeficiency virus; IGRA: Interferon gamma release assay.

changes. A repeat biopsy may help detect antacid bacilli. The diagnosis of primary nasal TB requires a combination of clinical presentation, seroconversion, Ziehl-Neelsen staining, and pathological biopsy. Positive Mtb culture results are considered the gold standard for diagnosis. However, the negative rate is high (50%–75%)[10], and conducting multiple cultures repeatedly can help increase the positivity rate. Additionally, when diagnosis is difficult, considering the local epidemiology of TB and the effectiveness of diagnostic anti-TB treatments is crucial[11]. Furthermore, differentiating this disease from other conditions such as midline granulomas (*i.e.*, granulomatosis with polyangiitis, leprosy, sarcoidosis, subcutaneous phycomycosis, and granulomatous syphilis) or neoplastic disorders (natural killer T-cell lymphoma, carcinoma)[12] is critical.

Notably, TST often yields false-negative results in immunocompromised patients; therefore, IGRA is the preferred method for TB screening during TNFi treatment. In clinical practice, screenings 3 and 6 months after the initial dosing and every six months thereafter is generally recommended. However, there is still no consensus on these guidelines. The risk of TB induced by monoclonal antibodies is significantly higher than that induced by etanercept, and the frequency of monitoring should be increased when economically feasible. Minimally invasive nasal surgery and HIV are high-risk factors that can diminish local immunity in the nasal cavity. In addition, diabetes can worsen the natural progression of immune-mediated diseases treated with biological therapies, thereby increasing the risk of nasal TB. Consequently, an increase in screening frequency is required.

CONCLUSION

In summary, we believe that when patients receiving TNFi therapy exhibit nasopharyngeal symptoms, it is crucial to be vigilant for nasal TB. Early completion of rhinoscopy and an appropriately increased frequency of IGRA monitoring, in conjunction with some key characteristics (Table 1), may aid in the early detection and diagnosis of primary nasal TB. However, determining the optimal frequency of TB screening by considering the socioeconomic factors is also necessary.

FOOTNOTES

Author contributions: Shen DX, Li C, and Ying ZH conceptualized and designed the research; Shen DX and Wang YW prepared the manuscript and contributed equally to this article, ensuring a cohesive presentation of the research findings; Lin ZM and Jin D were responsible for the meticulous analysis and interpretation of the case, providing essential insights that underpinned the study's conclusions; Li C and Ying ZH, as co-corresponding authors, were at the helm of conceptualizing and designing the research ideas, setting the stage for the study with their innovative and well-defined framework; Li C conceptualized, designed, and supervised the whole process of the project. He searched the literature, revised and submitted the early version of the manuscript. Ying ZH was instrumental and responsible for revision, table plotting, comprehensive literature search, preparation, and submission of the current version of the manuscript. All authors have read and approved the final manuscript, with Shen DX and Wang YW recognized as co-first authors for their significant contributions to the manuscript preparation, and the collaborative efforts of the team were instrumental in bringing the research to fruition.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Country of origin: China

ORCID number: Zhen-Hua Ying 0000-0002-5443-3675; Chen Li 0000-0002-8527-1680.

S-Editor: Liu JH
L-Editor: A
P-Editor: Zheng XM

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World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 November 26; 12(33): 6608-6612

DOI: 10.12998/wjcc.v12.i33.6608

ISSN 2307-8960 (online)

EDITORIAL

Journey to diagnosis: An unfinished exploration of IgG4-related sclerosing cholangitis

Ming-Xing Liang, Ya Chen, Ya He, Yi-Huai He

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade D
Creativity or Innovation: Grade D
Scientific Significance: Grade B

P-Reviewer: Kazi IA

Received: July 4, 2024
Revised: August 19, 2024
Accepted: August 23, 2024
Published online: November 26, 2024
Processing time: 84 Days and 12.2 Hours

Ming-Xing Liang, Ya Chen, Ya He, Yi-Huai He, Department of Infectious Diseases, Affiliated Hospital of Zunyi Medical University, Zunyi 563000, Guizhou Province, China

Corresponding author: Yi-Huai He, MD, Director, Department of Infectious Diseases, Affiliated Hospital of Zunyi Medical University, No. 149 Dalian Road, Huichuan District, Zunyi 563000, Guizhou Province, China. 993565989@qq.com

Abstract

IgG4-related sclerosing cholangitis (IgG4-SC) is an inflammatory disease that leads to bile duct stricture, characterized by the infiltration of IgG4-positive plasma cells into the bile duct wall, thickening of the bile duct wall, and narrowing of the lumen. The differential diagnosis of IgG4-SC mainly includes primary sclerosing cholangitis, cholangiocarcinoma, and pancreatic cancer. IgG4-SC is often associated with autoimmune pancreatitis and can be accurately diagnosed based on clinical diagnostic criteria. However, isolated IgG4-SC is difficult to distinguish from biliary tumors. Given the significant differences in biological behavior, treatment, and prognosis between these diseases, accurately identifying isolated IgG4-SC has very important clinical significance.

Key Words: Isolated IgG4-associated sclerosing cholangitis; Cholangiocarcinoma; Autoimmune pancreatitis; IgG4-related diseases; Diagnosis and differential diagnosis

Core Tip: Isolated IgG4-related sclerosing cholangitis (IgG4-SC) shares similar clinical manifestations to bile duct tumors, yet they differ significantly in biological behavior, treatment, and prognosis. Therefore, an accurate diagnosis of isolated IgG4-SC is crucial for the clinical management of patients. This article will delve into the key diagnostic points, difficulties, and challenges of isolated IgG4-SC to aid in better identifying and managing this disease.

Citation: Liang MX, Chen Y, He Y, He YH. Journey to diagnosis: An unfinished exploration of IgG4-related sclerosing cholangitis. *World J Clin Cases* 2024; 12(33): 6608-6612
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6608.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6608

INTRODUCTION

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of sclerosing cholangitis, featuring dense infiltration of IgG4-positive plasma cells and extensive fibrosis in the bile duct walls[1]. It is considered an immune-mediated inflammatory disease characterized by pancreaticobiliary inflammatory lesions, thickening of the bile duct wall, and extensive lymphocyte infiltration into the bile duct walls, leading to progressive narrowing and destruction of the bile ducts, along with elevated serum IgG4 levels[2].

This condition is a benign disease, and only a minority of patients who develop IgG4-SC will progress to liver cirrhosis or cholangiocarcinoma[3]. Currently, glucocorticoids are recommended as the first-line treatment for IgG4-SC[4], with a generally favorable prognosis for most patients. Early diagnosis and treatment of IgG4-SC remain crucial to prevent disease progression. Studies have shown that persistent inflammation leads to genomic instability and increases the risk of genetic mutations[5]. For instance, chronic inflammation drives the development of essential thrombocythemia through the activation of Janus kinase 2[6,7], further complicating the diagnosis of IgG4-SC. IgG4-SC is often associated with autoimmune pancreatitis (AIP) and is considered a biliary manifestation of IgG4-related disease (IgG4-RD)[2]. The clinical features of IgG4-SC include cholestatic manifestations such as jaundice and pruritus, however, these clinical presentations have poor specificity for diagnosing IgG4-SC. Therefore, the diagnosis of IgG4-SC is challenging, with a high risk of underdiagnosis or misdiagnosis. However, as time progresses and medical research delves deeper, corresponding diagnostic criteria have gradually been established. Nevertheless, diagnosing IgG4-SC still poses challenges at present.

The HISORt criteria, encompassing histology, imaging, serology, other organ involvement, and response to therapy, are frequently used in the United States and Europe to diagnose IgG4-SC or IgG4-associated cholangitis[8,9]. In 2012, the Japan Biliary Association established clinical diagnostic criteria for IgG4-SC[10]. In 2019, clinical practice guidelines for IgG4-SC were published[11]. Additionally, in 2022, a Japanese group proposed new clinical diagnostic criteria based on revisions to the 2012 clinical diagnostic standards[4], to address the shortcomings of the 2012 diagnostic criteria and provide more detailed diagnoses. When IgG4-SC is associated with AIP or other IgG4-RD, the diagnosis is relatively straightforward. However, diagnosing special types of IgG4-SC, such as isolated IgG4-SC, remains challenging[12,13]. These patients are sometimes misdiagnosed with cholangiocarcinoma and undergo unnecessary surgical resection.

THE DIAGNOSTIC CHALLENGES OF ISOLATED IGG4-SC

Serum IgG4 Levels are one of the most important markers for diagnosing IgG4-RD. However, in isolated IgG4-SC, serum IgG4 may be negative or slightly elevated, primarily presenting as obstructive jaundice with IgG4-positive plasma cell infiltration and frequent bile duct wall thickening[12,14]. These patients are sometimes misdiagnosed with cholangiocarcinoma and undergo surgical resection. Many researchers recommend endoscopic biopsy and immunostaining of tissue samples to determine the presence of IgG4, as this can provide strong diagnostic evidence[15], and is important for ruling out cholangiocarcinoma. However, obtaining sufficiently large characteristic pathological samples of IgG4-SC through endoscopic biopsy is challenging[16], as the obtained specimens are usually small and cannot be used to fully observe the entire range of lymphoplasmacytic sclerosing cholangitis. Additionally, studies have found IgG4-positive cells in primary sclerosing cholangitis (PSC) and cholangiocarcinoma. This finding indicates that relying solely on the detection of IgG4-positive cells as a specific diagnostic foundation may not be sufficient, as its specificity is highly controversial[17,18]. Therefore, the diagnosis of isolated IgG4-SC typically relies on imaging studies.

Ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic US (EUS), and intraductal US (IDUS) are used to assess bile duct abnormalities[19,20]. IgG4-SC associated inflammation most commonly affects the pancreaticobiliary segment, and is characterized by diffuse or segmental narrowing of the bile ducts with long segments of narrowing and upstream dilation[21]. Inflammation in IgG4-SC typically involves the entire thickness of the bile duct wall, particularly the submucosal and subserosal layers, with relatively less damage to the epithelial layer[22]. In contrast, PSC cholangiography usually shows band-like strictures, beaded or pruned tree appearance, and diverticulum-like changes[23], and cholangiocarcinoma originates from the epithelial layer and is characterized by its invasive growth. Contrast-enhanced CT reveals that a hallmark of IgG4-SC is the uniform enhancement of the bile duct walls during the arterial phase, whereas in cholangiocarcinoma, the bile duct wall exhibits dual-layer enhancement. The smoothness of the inner lumen and outer layer are also characteristic of IgG4-SC[24,25]. Although differential diagnosis using CTs or MRIs poses certain challenges, an advantage lies in the ability to detect tumor invasion and extrabiliary metastatic lesions. US results are nonspecific and cannot differentiate IgG4-SC from PSC or cholangiocarcinoma[26]. EUS or IDUS offer higher resolution, with EUS also aiding in obtaining tissue samples[27,28]. IDUS can display the stratified structure of the bile duct wall with high resolution, showing characteristics including circular symmetric wall thickening, smooth inner and outer edges, and uniform internal echoes at the site of biliary strictures. Additionally, wall thickening in non-strictured areas is also characteristic of IgG4-SC[16,29,30], thus IDUS can relatively clearly reflect the pathological differences between IgG4-SC, PSC, and cholangiocarcinoma. After imaging examinations, two aspects should be evaluated: Characteristic cholangiographic features and bile duct wall thickness[11]. Characteristic cholangiographic features may help differentiate IgG4-SC from PSC. Cholangiography is useful for the differential diagnosis of diffuse strictures. However, in cases with localized strictures, diagnosing based on cholangiographic features alone has certain limitations. Nevertheless, for cases with localized strictures, endoscopic biopsy through the Vater's papilla is essential to rule out cholangiocarcinoma, although the sensitivity for detecting malignant tumors (55%-72%) is relatively low[11].

In patients with isolated IgG4-SC that are difficult to diagnose, a steroid trial may also be considered to assist in diagnosis. This involves assessing the resolution of findings on cholangiographic images obtained through CT/endoscopic retrograde cholangiopancreatography (ERCP)/magnetic resonance cholangiopancreatography after administering a steroid dose of 0.4-0.6 mg/kg for 1 or 2 weeks. If there is no improvement, a reevaluation is necessary to consider other possible diseases[11]. Before and after the commencement of steroid treatment, regular follow-ups are required to assess symptoms and signs, perform blood biochemical tests, measure IgG/IgG4 Levels, and conduct imaging studies. Additionally, attention must be paid to signs of relapse, the exclusion of malignant lesions, and the management of adverse reactions to steroids[11].

In recent years, research has discovered that Annexin A11 serves as an autoantigen in both IgG4-SC and AIP[31]. Additionally, Yukari Kato and colleagues reported a case of IgG4-SC diagnosed through the detection of antibodies against laminin 511-E8, despite normal serum IgG4 concentrations and no evidence of IgG4 plasma cell infiltration in the bile ducts[32]. A prospective study found that IgE levels can be utilized for diagnosing and predicting relapses in IgG4-RD[33]. Furthermore, studies have identified potential biomarkers such as serum IFN-α[34], peripheral plasmablast counts in treatment-naive IgG4-RD patients[35], the ratio of peripheral $CD19^{+}CD24^{-}CD38^{hi}$ subset/$CD19^{+}$ B cells in IgG4-RD patient[36], and PD-1^{+} Tfh cell counts[37] for diagnosing and monitoring the activity of IgG4-SC. However, further research is needed to confirm whether these indicators can become new specific biomarkers for IgG4-SC.

CONCLUSION

As most IgG4-SC cases are associated with AIP, IgG4-SC can be accurately diagnosed based on clinical diagnostic criteria. However, the differential diagnosis of isolated IgG4-SC currently remains challenging, especially in distinguishing it from cholangiocarcinoma, PSC, and pancreatic cancer. Methods such as CT, MRI, ERCP, IDUS, bile duct biopsy, and duodenal papilla biopsy aid in the diagnosis and differential diagnosis of isolated IgG4-SC. When these examination results do not show typical changes or when steroid treatment is ineffective, reevaluation may be necessary, potentially including pathological examination or surgery. The use of serum biomarkers discovered in recent research studies can also be considered to assist in diagnosis. Therefore, improving the diagnostic level of IgG4-SC depends on further research into its etiology and pathogenesis.

FOOTNOTES

Author contributions: He YH, Liang MX, Chen Y and He Y contributed to this paper; He YH and Liang MX designed the overall concept and outline of the manuscript, contributed to the writing, and editing the manuscript, and review of literature; Chen Y and He Y contributed to the discussion and design of the manuscript.

Supported by The Science and Technology Research Foundation of Guizhou Province, and Zunyi City, No. QKHJC-ZK (2022) YB642, No. ZSKH-HZ (2022) 344, and No. gzwjkj2021-071; The WBE Liver Fibrosis Foundation, No. CFHPC2025028; and The Beijing Gandan Phase Mutual Public Welfare Fund for Artificial Liver Project, No. iGandanF-1082024-Rgg018.

Conflict-of-interest statement: The authors declare that they have no conflict of interests.

Country of origin: China

ORCID number: Ming-Xing Liang 0009-0002-4371-951X; Ya Chen 0000-0002-5618-8124; Ya He 0009-0002-4173-5399; Yi-Huai He 0000-0002-8639-3436.

S-Editor: Liu H
L-Editor: A
P-Editor: Chen YX

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World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 November 26; 12(33): 6613-6619

DOI: 10.12998/wjcc.v12.i33.6613

ISSN 2307-8960 (online)

MINIREVIEWS

Current evidence on artificial intelligence in regional anesthesia

Bhanu Pratap Swain, Deb Sanjay Nag, Rishi Anand, Himanshu Kumar, Pradip Kumar Ganguly, Niharika Singh

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade A

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade A, Grade B

P-Reviewer: Liang P; Qin XR

Received: June 18, 2024

Revised: September 11, 2024

Accepted: September 19, 2024

Published online: November 26, 2024

Processing time: 100 Days and 20.2 Hours

Bhanu Pratap Swain, Deb Sanjay Nag, Rishi Anand, Himanshu Kumar, Pradip Kumar Ganguly, Niharika Singh, Department of Anaesthesiology, Tata Main Hospital, Jamshedpur 831001, India

Bhanu Pratap Swain, Rishi Anand, Himanshu Kumar, Department of Anesthesiology, Manipal Tata Medical College, Jamshedpur 831017, India

Co-first authors: Bhanu Pratap Swain and Deb Sanjay Nag.

Corresponding author: Deb Sanjay Nag, MD, Doctor, Department of Anaesthesiology, Tata Main Hospital, C Road West, Northern Town, Bistupur, Jamshedpur 831001, India. ds.nag@tatasteel.com

Abstract

The recent advancement in regional anesthesia (RA) has been largely attributed to ultrasound technology. However, the safety and efficiency of ultrasound-guided nerve blocks depend upon the skill and experience of the performer. Even with adequate training, experience, and knowledge, human-related limitations such as fatigue, failure to recognize the correct anatomical structure, and unintentional needle or probe movement can hinder the overall effectiveness of RA. The amalgamation of artificial intelligence (AI) to RA practice has promised to override these human limitations. Machine learning, an integral part of AI can improve its performance through continuous learning and experience, like the human brain. It enables computers to recognize images and patterns specifically useful in anatomic structure identification during the performance of RA. AI can provide real-time guidance to clinicians by highlighting important anatomical structures on ultrasound images, and it can also assist in needle tracking and accurate deposition of local anesthetics. The future of RA with AI integration appears promising, yet obstacles such as device malfunction, data privacy, regulatory barriers, and cost concerns can deter its clinical implementation. The current mini review deliberates the current application, future direction, and barrier to the application of AI in RA practice.

Key Words: Artificial intelligence; Regional anesthesia; Machine learning; Ultrasonography; Nerve block

Core Tip: Proficiency in ultrasound-guided regional anesthesia (UGRA) demands an accurate interpretation of sono-anatomy and precise delivery of local anesthetics in the intended location by maneuvering a block needle. Integration of artificial intelligence (AI) can make the job of clinicians a lot easier by deciphering the correct anatomy and providing real-time needle guidance. It promises to improve the success of the UGRA procedures and reduce the complication rate by minimizing human error. Furthermore, AI can be a great tool in education and training. It can help the trainees to learn regional anesthesia techniques faster and more efficiently. Although the future looks promising, the full integration of AI in clinical practice needs user validation and ample data on clinical outcomes.

Citation: Swain BP, Nag DS, Anand R, Kumar H, Ganguly PK, Singh N. Current evidence on artificial intelligence in regional anesthesia. *World J Clin Cases* 2024; 12(33): 6613-6619
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6613.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6613

INTRODUCTION

Before the advent of ultrasound in regional anesthesia (RA), peripheral nerve blocks (PNBs) were traditionally practiced with landmark-based techniques for anatomic guidance[1]. Ultrasound guidance has transformed the practice of RA, making it safer and more successful. With the ability to visualize nerves, muscle planes, blood vessels, and needles in real time, ultrasound-guided RA (UGRA) provides exceptional accuracy and precision[1]. However, mastering the skill of UGRA is not an easy feat. It requires extensive training, a deep understanding of sono-anatomy, and good hand-eye coordination. The learning curve can be steep, and trainees often struggle with ultrasound image acquisition and needle tracking[2]. These challenges are especially pronounced in cases involving obese patients, those with tissue edema, and deep-seated nerve plexuses[3]. Recent developments in echogenic needles and needle guidance systems have improved needle visibility[4]. Despite these advancements, there is still limited development in improving the quality of ultrasound images and their interpretation. With artificial intelligence (AI) integration, we can overcome these challenges and improve the safety and success of UGRA procedures.

AI is revolutionizing the medical field, providing clinicians with crucial support to deliver swift, effective treatment to their patients[5]. With AI technology, machines and computers can mimic human intelligence and problem-solving abilities, overcoming common human limitations such as fatigue and loss of attention. AI can interpret things that the human eye may struggle to decipher or take a long time to do so.

In RA, AI-guided solutions can play a critical role in enhancing the success rate of procedures and minimizing complications. AI can assist clinicians with ultrasound image interpretation by highlighting relevant anatomical structures and providing guidance in needle insertion, advancement, and injection of local anesthetics[6]. It can also facilitate the training of novice clinicians in UGRA techniques, allowing them to acquire the required skills quickly and efficiently, reducing the learning curve associated with the procedure[7].

The use of AI technology for ultrasound-guided PNBs and neuraxial blocks has enormous potential. Nonetheless, before implementing these AI models in clinical settings, they must undergo real-case scenario studies to ensure their validity, utility, and safety.

FUNDAMENTALS OF AI

AI technology is based on two fundamental concepts-machine learning (ML) and deep learning (DL). ML involves training computers to learn from data and algorithms, improving their performance over time. It requires exposure to training data and algorithms to identify patterns and improve decision-making. On the other hand, DL is a subset of ML that uses multi-layered neural networks, called deep neural networks, to perform complex decision-making. These networks are structured similarly to the human brain, enabling them to identify patterns and relationships, recognize phenomena, evaluate different possibilities, and make predictions and decisions. A convolutional neural network (CNN) is a type of DL algorithm that is particularly useful in tasks that involve recognizing and processing images. The architecture of CNN is based on the way the human brain processes visual information. By training on large amounts of data, CNN can learn to recognize patterns and features that are associated with specific objects or classes. This makes them especially valuable in the field of medical imaging, where CNN can help clinicians quickly and accurately identify abnormalities[8]. Although AI is revolutionizing healthcare, there are challenges to overcome before we realize its full potential. The availability of quality medical data in accordance with data security and privacy concerns would be critical to achieving the desired outcomes. Although AI-guided clinical therapy may appear evidence-based and realistic, hallucinations can create a false narrative necessitating human involvement for appropriate care delivery[8].

Scope of AI in ultrasound guided RA

Performing RA with the help of ultrasound guidance is a complex multitasking process that involves many steps. These steps include placing the ultrasound probe in the area of interest, acquiring the correct image, deciding where to insert

the needle, inserting the needle correctly, adjusting the ultrasound probe to see the needle tip, administering the drug, checking that the anesthetic is spreading correctly, monitoring for complications, and finally assessing the effectiveness of the block. To carry out these tasks, practitioners should have a solid understanding of anatomy and good hand-eye coordination. For novice practitioners and trainees, it can be overwhelming. AI can now assist or supervise all these steps using information from clinicians, patients, and procedures. Some of the current AI-assisted technologies used in UGRA are real-time anatomic guidance, target detection, and needle tracking[7].

AI-assisted real time anatomic guidance in UGRA

Ultrasound images are currently available in two dimensions (2D) and grayscale. Anatomical structures appear in varying shades of grey based on the tissue's echogenicity. Moreover, the human interpretation of the greyscale ultrasound images is nonintuitive and limited by experience. AI can overcome this challenge by highlighting the anatomical structures and providing a visual cue to the operator, making it easier to focus on the intended structure. One of the most common AI technologies used to process ultrasound images is segmentation, where color overlays of various sono-anatomical features are used to differentiate relevant anatomic structures[9-13]. Other less common methods include using bounding boxes around the intended structure, displaying expanding circular rings from the center of the nerve plexus, and putting name tags over the structure in question[14,15].

AI can also help the operator in getting the best ultrasound image of the intended structures during the ultrasound scanning phase of the PNBs. Some known methodologies include displaying successful scan indicators[13,16], specifying optimal *vs* non-optimal images[17], creating a three-dimensional (3D) model of the scanned image[18], and guidance in probe[10] manipulation to get the ideal image. AI solutions are also available for ultrasound-guided central neuraxial blocks that can significantly improve the first-pass success rate and reduce complications. Common techniques include identifying the vertebral level, outlining the distance from the skin to the posterior complex or epidural space, structure identification by segmentation or bounding boxes, and marking the optimal needle insertion point[19-22].

AI models for PNBs

Currently, there are few commercially available AI solutions for ultrasound guided PNBs. One of the most studied models is the "ScanNav Anatomy Peripheral Nerve Block" (manufactured by Intelligent Ultrasound, Cardiff, United Kingdom)[23]. It helps in image interpretation by providing a color overlay of key sono-anatomical structures in 10 commonly performed PNBs (interscalene, supraclavicular, superior trunk, axillary, erector spinae, suprainguinal fascia-iliaca, femoral, adductor canal, and popliteal nerve block). This technology uses CNN, an advanced DL based on U-Net architecture to delineate anatomical structures in real-time ultrasound. A database of 80000 ultrasound images is used by the algorithm as a reference for labeling the sono-anatomical structures in the view. The ScanNav technology has recently undergone many validation studies in clinical settings involving experts, non-experts, and trainees[6,9,11,24,25]. All the studies have concluded that ScanNav AI-based technologies have tremendous potential to help non-experts and experts in RA practice.

NerveBlox, manufactured by Smart Alfa Teknoloji San. Ve Tic. A.S. in Ankara, Turkey, is an AI-powered solution for PNBs similar to ScanNav. This device utilizes real-time ultrasound images and a CNN algorithm to label (color overlay) important anatomical landmarks like muscles, nerves, bones, and blood vessels. It supports 12 types of nerve blocks such as inter-scalene brachial plexus block, superficial cervical plexus block, supraclavicular brachial plexus block, infraclavicular brachial plexus block, axillary brachial plexus block, pectoralis nerve blocks, transversus abdominis plane block, erector spinae plane block, rectus sheath block, femoral nerve block, adductor canal block, and popliteal sciatic nerve block[26]. A few studies have validated Nerveblox AI software as a handy tool for real-time decision-making during PNBs procedures[13,15,16]. Both Nerveblox and ScanNav are external devices with a separate display screen that needs to be plugged into a compatible ultrasound machine to function.

Some of the other commercially available AI devices for PNBs are cNerve (GE Healthcare, Chicago, IL, United States)[27], NerveTrack (Samsung, Suwon, South Korea)[28], and Smart Nerve (Mindray, Shenzhen, China)[29].

AI models for central neuraxial block

There are two AI systems available that can assist with central neuraxial block (CNB) procedures. One of these is Accuro, a handheld device manufactured by Rivanna Medical (Charlottesville, VA, United States)[30]. This device uses SpineNav3D AI-Based Spine Recognition technology to automatically detect bony landmarks and provide a real-time 3D view of the scan plane. It accurately determines the depth of the epidural space and offers real-time tracking of the needle [30]. Studies have shown that Accuro can reduce the number of needle redirects and increase the chances of first-pass success[22,31-34]. The other AI-enabled software is uSINE, manufactured by HiCura Medical (Singapore). It is designed for automatic identification of spinal level and needle guidance during ultrasound guided CNBs[35]. USINE is an external device that must be connected to a compatible ultrasound machine. The software guides the operator in achieving an ideal ultrasound view. Once the desired view is obtained, the operator marks the skin puncture site and then performs the neuraxial procedure by introducing the needle through the marked site. However, real-time needle tracking is not available with this software. One study reported a 92% first attempt of dural puncture success during spinal anesthesia in 100 obstetric patients when uSINE was used to identify the surface landmark[36].

Role of AI in training

Mastering the safe performance of RA can be a challenging task for trainees due to the steep learning curve involved. However, the advent of AI-assisted technologies has paved the way for an easier and more efficient training process. With multiple AI-integrated devices available on the market, trainees can now easily overcome the difficulties they face

while learning RA. These devices can highlight key anatomical structures and reconstruct 3D anatomy from 2D ultrasound images, making it easier for trainees to visualize 3D anatomy. Augmented reality (AR) has revolutionized simulation-based training, enabling trainees to improve hand-eye coordination, positioning, and dexterity issues during needle manipulation[37,38]. Devices like Needle Trainer™, manufactured by Intelligent Ultrasound (Cardiff, United Kingdom), provide a non-invasive simulation of needle manipulation on a live participant using a retractable needle and a superimposed virtual image on the ultrasound scan[39,40]. The AR experience can be further enhanced by providing haptic feedback to the operator, which gives the feel of a real needle and tissue. The Regional Anesthesia Simulator and Assistant is another AI-based simulator that offers a virtual reality environment with haptic feedback for needle manipulation in RA procedures[41]. With such advanced technology at their disposal, trainees can now learn RA more efficiently and safely, without compromising on patient safety.

Furthermore, real-time feedback during training can significantly improve the learning process of RA. Recently, eye-tracking technology has been studied in UGRA to assess visual attention to relevant anatomical structures and decision-making between experts and novices[42,43]. The study found that experts tend to focus more on clinically relevant sono-anatomical features while novices struggle to do so. By integrating AI with eye-tracking technology, trainees can be reminded to focus during live procedures, which can accelerate their learning process. Similarly, a study was conducted on hand motion analysis during the performance of UGRA by both experts and trainees. The imperial college surgical assessment device, which is a validated measure of hand movement during surgical training, was used to monitor hand movement during the scanning and needling phases of UGRA. The study concluded that experts performed significantly better than the trainees[44]. A recent study used Onvision needle tip tracking technology (B Braun Melsungen AG, Melsungen, Germany) to analyze procedure time, hand movement, and path length during simulated ultrasound-guided PNBs procedures in a porcine phantom model[45]. The study showed a significant reduction in procedure time and hand movement for out-of-plane techniques when this new technology was used compared to when it was not. A similar study on human volunteers for ultrasound-guided lumbar plexus block demonstrated reduced hand movements and path lengths[46]. Hence, AI technology can utilize the data from these devices to improve trainee performance during training.

Table 1 summarizes the currently available commercial devices for PNBs and central neuraxial blocks[23,26-30,35,40,45]. Realtime analysis of ultrasound images through AI algorithms by highlighting key anatomical structures can enhance their visualization and minimize the risk of accidental puncture of key vital structures. AI guided precise needle placement can potentially lead to higher rates of successful blocks, enhanced pain management and faster recovery. Similarly fewer complications like hematoma, nerve damage and infection would also translate into better outcomes.

Constraints in integration of AI in RA

AI has displayed remarkable potential in the field of RA and is growing at an accelerated pace. However, the complete implementation of AI in clinical practice has several challenges.

Currently, numerous AI-enabled devices or models are available, but only a few have undergone external validation. The paucity of data on patient outcomes utilizing these devices and the unstructured and heterogeneous literature available are further challenges. Besides, the absence of standards to verify the accuracy and utility of these devices constitutes a significant impediment to their incorporation into clinical practice[47].

Effective ML relies on thorough training with vast and diverse datasets. However, the availability and quality of patient data remain a significant concern that can hinder the advancement of AI. Transfer learning emerges as a valuable method to tackle this challenge by leveraging knowledge gained from one domain and applying it to another[48]. Furthermore, if the input data is flawed, the AI model's output will contain inaccuracies, potentially posing a serious impact on the efficacy and safety of medical procedures[49]. Additionally, the ethical and legal aspects, along with privacy concerns stemming from such data, need to be carefully addressed. The Alan Turing Institute, a leading center for data science and AI, has developed comprehensive guidelines for ethics and safety in this domain and needs to be referred to whenever dealing with ethical matters related to patient data management[50].

Though AI-assisted devices possess tremendous abilities, they may fail, just like any other technology. Misidentification of anatomy and the AI model's emphasis on the wrong features may lead to undesired outcomes. The accuracy of AI in specific populations, such as pediatric age groups, geriatric populations, and patients with altered anatomy, is not well-studied[7]. Therefore, over-reliance on AI assistance has downsides, particularly with trainees and learners who lack confidence in their knowledge of anatomy. A thorough knowledge of relevant anatomy is essential. It is advisable not to replace traditional expert mentoring with AI-assisted devices, and trainees should learn standard techniques of ultrasound image acquisition before exposure to AI-assisted devices.

The implementation of AI is further hindered by the high costs associated with it. However, as the usage of this technology becomes more widespread, the costs are expected to decrease gradually, making it more affordable and accessible to all in the long run.

AI in RA represents a multidisciplinary field that thrives on collaboration between clinicians, engineers, and administrators. It's imperative to align these disciplines to ensure the successful integration of AI in RA. Regulatory authorities should play a pivotal role in establishing policies that promote the ethical sharing of data across disciplines and institutes. This approach will not only foster the rapid advancement of AI technology but also accelerate its seamless integration into clinical anesthesia practice.

These challenges can only be overcome by collaborating and data-sharing between healthcare institutes and research centers by ensuring the availability of diverse yet representative datasets. Rigorous validation in various clinical settings across geographic locations would help standardize and benchmark evaluation metrics to compare different models. A multidisciplinary approach involving industry, clinicians, researchers, regulatory bodies, and experts in biomedical ethics is the key to unlocking the complete potential of AI in RA.

Table 1 Commercially available devices

Device name	Manufacturer	Features	Remarks
ScanNav Anatomy Peripheral Nerve Blocks [23]	Intelligent Ultrasound, Cardiff, United Kingdom	Color overlay of key sono-anatomical structures in 10 commonly performed peripheral nerve blocks	Plug-and-play device, compatible with selected ultrasound machines
Nerve blox[26]	Smart Alfa Teknoloji San. Ve Tic. A.S. in Ankara, Turkey	Color overlay of anatomical landmarks and supports 12 types of nerve blocks	Plug-and-play device, compatible with selected ultrasound machines
Nerve track[28]	Samsung, Suwon, South Korea	Yellow box around the nerves	In-built AI feature in the ultrasound machine
Smart nerve[29]	Mindray Shenzhen, China	Color overlay of neural structures, real-time needle navigation based on 3D magnetic field technology	In-built AI feature in the ultrasound machine
CNerve[27]	GE Healthcare, Chicago, IL, United States	Highlights the target nerve to distinguish it from surrounding anatomical structures	AI feature in-built in ultrasound machine
Accuro[30]	Rivanna Medical Charlottesville, VA, United States	Provide a real-time 3D view of spine with accurate determination of the depth of epidural space	Handheld device
USINE[35]	HiCura Medical Singapore	Realtime identification of spinal level during central neuraxial blocks by using name tags	Plug-and-play device, compatible with most ultrasound probes
Needle Trainer™[40]	Intelligent Ultrasound Cardiff, United Kingdom	Provides non-invasive simulation of needle manipulation on a live participant	Do not provide haptic feedback of needle manipulation
Onvision® Needle Tip Tracking[45]	B Braun Melsungen AG, Melsungen, Germany	Onvision accurately indicates the needle tip position inside the body both in and out of the ultrasound viewing plane	Exclusively works with Philips Xperius ultrasound system

AI: Artificial Intelligence; 3D: Three-dimensional.

Being a relatively new development with significant potential, AI models are slowly getting integrated into commercially available ultrasound machines for PNBs and central neuraxial blocks. It can potentially shorten procedure times and ensure financial benefits. Similarly, precise needle placement and drug deposition can potentially result in reduced complications, faster recovery, and reduced healthcare costs. However, with widespread adoption and value realization, the cost of hardware and software for AI in RA is expected to steadily decrease over the next few years.

CONCLUSION

Initial reports suggest that AI applications have tremendous potential to be a game-changer in RA. Currently, several AI models are available for peripheral and central neuraxial blocks. Most of these models use deep neural networks trained on large amounts of data to assist clinicians in real-time decision-making by aiding in image interpretation and needle tracking. Additionally, AI can revolutionize education and training in RA, making simulation-based training more pragmatic and intuitive, thus enabling trainees to learn faster. However, some barriers still exist in its assimilation into clinical practice. The common impediments include insufficient patient data on the use of these devices, lack of standardization, and ethical concerns. Clinicians, scientists, and policymakers must coordinate and standardize the technology to overcome these barriers.

In conclusion, a new era of AI-assisted RA has begun. Anaesthesiologists should embrace this new technology and enhance their skills, reduce the learning curve, and provide better patient care by leveraging AI-guided solutions for RA.

FOOTNOTES

Author contributions: Swain BP, Nag DS, and Anand R designed the overall concept and outline of the manuscript; Kumar H, Ganguly PG, and Singh N contributed to the discussion and design of the manuscript; Swain BP, Nag DS, Anand R, Kumar H, Ganguly PK, and Singh N contributed to the writing, and editing the manuscript and review of literature; all of the authors read and approved the final version of the manuscript to be published.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

Country of origin: India

ORCID number: Deb Sanjay Nag 0000-0003-2200-9324.

Corresponding Author's Membership in Professional Societies: Indian Society of Anaesthesiology, No. S2863.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zheng XM

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World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 November 26; 12(33): 6620-6628

DOI: 10.12998/wjcc.v12.i33.6620

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Risk factors and risk prediction model for mucocutaneous separation in enterostomy patients: A single center experience

Yun Liu, Hong Li, Jin-Jing Wu, Jian-Hong Ye

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D

Novelty: Grade B

Creativity or Innovation: Grade C

Scientific Significance: Grade D

P-Reviewer: Kita K

Received: May 20, 2024

Revised: September 5, 2024

Accepted: September 11, 2024

Published online: November 26, 2024

Processing time: 130 Days and 1.8 Hours

Yun Liu, Hong Li, Jin-Jing Wu, Department of Reconstructive, Hand and Plastic Surgery, Zhejiang Chinese Medical University, Lishui Central Hospital, 289 Kuocang Road, Liandu District, Lishui 323000, Zhejiang Province, China

Jian-Hong Ye, Department of Operation Room, Zhejiang Chinese Medical University, Lishui Central Hospital, 289 Kuocang Road, Liandu District, Lishui 323000, Zhejiang Province, China

Corresponding author: Jian-Hong Ye, MSc, Department of Operation Room, Zhejiang Chinese Medical University, Lishui Central Hospital, 289 Kuocang Road, Liandu District, Lishui 323000, Zhejiang Province, China. 442339139@qq.com

Abstract

BACKGROUND

Mucocutaneous separation (MCS) is a common postoperative complication in enterostomy patients, potentially leading to significant morbidity. Early identification of risk factors is crucial for preventing this condition. However, predictive models for MCS remain underdeveloped.

AIM

To construct a risk prediction model for MCS in enterostomy patients and assess its clinical predictive accuracy.

METHODS

A total of 492 patients who underwent enterostomy from January 2019 to March 2023 were included in the study. Patients were divided into two groups, the MCS group (n = 110), and the non-MCS (n = 382) based on the occurrence of MCS within the first 3 weeks after surgery. Univariate and multivariate analyses were used to identify the independent predictive factors of MCS and the model constructed. Receiver operating characteristic curve analysis was used to assess the model's performance.

RESULTS

The postoperative MCS incidence rate was 22.4%. Suture dislodgement (P < 0.0001), serum albumin level (P < 0.0001), body mass index (BMI) (P = 0.0006), hemoglobin level (P = 0.0409), intestinal rapture (P = 0.0043), incision infection (P < 0.0001), neoadjuvant therapy (P = 0.0432), stoma site (P = 0.0028) and elevated intra-abdominal pressure (P = 0.0395) were potential predictive factors of MCS. Suture dislodgement [P < 0.0001, OR: 28.0075 95%CI: (11.0901-82.1751)], serum

albumin level (P = 0.0008, OR: 0.3504, 95%CI: [0.1902-0.6485]), BMI [P = 0.0045, OR: 2.1361, 95%CI: (1.2660-3.6235)], hemoglobin level [P = 0.0269, OR: 0.5164, 95%CI: (0.2881-0.9324)], intestinal rapture [P = 0.0351, OR: 3.0694, 95%CI: (1.0482-8.5558)], incision infection [P = 0.0179, OR: 0.2885, 95%CI: (0.0950-0.7624)] and neoadjuvant therapy [P = 0.0112, OR: 1.9769, 95%CI: (1.1718-3.3690)] were independent predictive factors and included in the model. The model had an area under the curve of 0.827 and good clinical utility on decision curve analysis.

CONCLUSION

The mucocutaneous separation prediction model constructed in this study has good predictive performance and can provide a reference for early warning of mucocutaneous separation in enterostomy patients.

Key Words: Enterostomy; Mucocutaneous separation; Risk assessment model; Performance validation

Core Tip: In this study a risk prediction model for mucocutaneous separation in enterostomy patients was developed, identifying key predictive factors such as suture dislodgement, serum albumin levels, and body mass index. The model demonstrated strong predictive accuracy with an area under the curve of 0.827, offering a valuable tool for early intervention and improved patient outcomes in clinical practice.

Citation: Liu Y, Li H, Wu JJ, Ye JH. Risk factors and risk prediction model for mucocutaneous separation in enterostomy patients: A single center experience. *World J Clin Cases* 2024; 12(33): 6620-6628
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6620.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6620

INTRODUCTION

Enterostomy is one of the most commonly performed surgeries by gastrointestinal surgeons. It involves temporary or permanent diversion of the patient's intestinal tract to an artificial opening (stoma) in the abdominal wall as a means of excreting intestinal contents[1]. According to statistics, hundreds of thousands of people worldwide undergo enterostomy surgery each year due to conditions such as inflammation, trauma, or intestinal cancer, with the number of patients undergoing ostomy surgery in China exceeding one hundred thousand annually, and the total number currently exceeding one million[2]. However, enterostomy also imposes varying degrees of physiological and psychological burdens on patients, severely affecting their quality of life and imposing significant economic burdens on families and society[3,4]. Leakage of intestinal contents after enterostomy surgery can lead to serious complications, with reported complication rates ranging from 10% to 50%[5,6]. Mucocutaneous separation (MCS) of enterostomy is one of the common early complications following enterostomy surgery, with its occurrence frequency accounting for 4% to 24% of enterostomy surgery complications[7].

MCS, the separation of the edge of the intestinal stoma mucosa from the sutured area of the abdominal wall skin, commonly occurs within 1 to 3 weeks after surgery. Incomplete tissue healing at the suture site results in an open wound between the mucosa and the skin[7]. The overall incidence rate of MCS outside China ranges from 3.7% to 9.7%[8,9], while in China, it is reported to be 16.33%[10]. MCS often leads to a series of adverse reactions of varying degrees, including acute peritonitis, incision infection, and stoma retraction. Additionally, scarring produced after the healing of MCS can cause stoma stenosis or retraction[11]. When MCS occurs, the reduced adhesion effect at the separation site impairs the healing process, not only slowing down wound healing but also increasing damage to the skin around the stoma. The occurrence of MCS after enterostomy prolongs the patient's hospital stay, causing physical and psychological distress to patients while dramatically increasing the difficulty, satisfaction, and workload of nursing care. Therefore, early detection and management of MCS post-enterostomy are of paramount importance for patients, their families, and healthcare providers.

Previous studies on MCS vary in terms of included variables and sample sizes, with most being retrospective studies and controversial in their conclusions. To date, there have been no reports on the establishment of a risk assessment model for MCS. This study aims to explore risk factors for MCS, establish a risk prediction assessment model, and assess the accuracy of the model.

MATERIALS AND METHODS

Participants

A prospective cohort was established, including patients who underwent enterostomy at our center from January 2019 to March 2023. Participants were included based on the following inclusion criteria: Patients determined to need

enterostomy after admission; Aged 18 years and above; Patients without mental disorders, capable of normal communication and interaction; Able to maintain regular contact for follow-up. Participants were excluded based on the following exclusion criteria: Had prior abdominal surgery; Occurrence of severe complications such as pulmonary embolism, myocardial infarction, or stroke after surgery; critically ill or deceased patients; Were lost to follow-up. This study was approved by the ethics committee of our hospital. All participants provided informed consent.

Mucocutaneous separation assessment

An expert team consisting of ten experienced gastroenterologists was set up to evaluate participants' clinical presentation to determine whether MCS had occurred or not. All members of the team were blinded by the research objectives and details.

Determination of MCS was based on expert consensus[12] and relevant guidelines[13]. The criteria for defining MCS, its clinical manifestations, and predisposing factors were summarized in the assessment criteria for MCS. Predisposing factors were defined as poor peristomal tissue healing resulting in an open wound between the skin and mucosa. A normal stoma exhibits glossiness, redness, and slight convexity, with tight adhesion between the peristomal mucosa and skin. The surrounding skin color is normal and intact. Clinical symptoms of MCS include varying degrees of separation depth ranging from 1 to 1.4 cm within the subcutaneous abdominal wall layers. White or yellowish odorless fluid may exude from the separation site.

Statistical analysis

Statistical analysis was conducted using R version 4.1.1. Continuous data are presented as mean ± SD and were compared between groups using the independent sample *t*-test. Categorical data are reported as absolute numbers and percentages. Categorical variables were compared using the χ^2 test. Univariable logistic regression was used to identify potential predictive factors of MCS and multivariate logistic regression was then used to identify independent predictors of MCS. The independent predictors were then used to construct a binomial logistic predictive model. Receiver operating characteristic (ROC) curve analysis was also used to evaluate the model's performance. Decision curve analysis (DCA) was used to assess the utility of the model. The model was expressed as a nomogram. *P* values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

A total of 548 participants were initially included, however, 56 were excluded due to being critically ill (n = 6), deceased (n = 12), or having prior abdominal surgery (n = 38). In total, 492 participants were included. The mean age was 62.0 ± 13.56 years. One hundred and eighty-seven (38%) of the participants were female and 305 (62%) were male. The most common indication for enterostomy in the cohort was colorectal tumors, accounting for 412 (75.2%) of all cases. The main sites of enterostomy were ileostomy (63.2%) and colostomy (36.8%). Participants in the study group were assigned to the MCS Group (n = 110) and the non-MCS Group (n = 382). The median occurrence of MCS was 16.1 (7–25) days after surgery. Body mass index (BMI) (P = 0.007), enterostomy site (P = 0.003), suture dislodgement (P < 0.001), elevated intra-abdominal pressure (P = 0.001), and incision infection (P < 0.001) were significantly different between the two groups. There were significant differences between the two groups with respect to other variables. The baseline characteristics of the participants are summarized in Table 1.

Predictive factors of MCS and the nomogram

Based on the univariate logistic regression analysis, suture dislodgement (P < 0.0001), serum albumin level (P < 0.0001), BMI (P = 0.0006), hemoglobin level (P = 0.0409), intestinal rapture (P = 0.0043), incision infection (P < 0.0001), neoadjuvant therapy (P = 0.0432), stoma site (P = 0.0028) and elevated intra-abdominal pressure (P = 0.0395) were determined to be potential predictive factors of MCS. These were included in the multivariate logistic regression analysis. Following multivariate logistic regression analysis, suture dislodgement [P < 0.0001, OR: 28.0075 95%CI: (11.0901-82.1751)], serum albumin level [P = 0.0008, OR: 0.3504, 95%CI: (0.1902-0.6485)], BMI [P = 0.0045, OR: 2.1361, 95%CI: (1.2660-3.6235)], hemoglobin level [P = 0.0269, OR: 0.5164, 95%CI: (0.2881-0.9324)], intestinal rapture [P = 0.0351, OR: 3.0694, 95%CI: (1.0482-8.5558)], incision infection [P = 0.0179, OR: 0.2885, 95%CI: (0.0950-0.7624)] and neoadjuvant therapy [P = 0.0112, OR: 1.9769, 95%CI: (1.1718-3.3690)] were determined to be independent predictive factors of MCS. The results of univariate and multivariate logistic regression analysis are presented in Table 2.

Based on the factors identified above, we constructed first a logistic model including only the independent predictive factors (suture dislodgement, serum albumin level, BMI, hemoglobin level, intestinal rapture, incision infection and neoadjuvant therapy) to predict MCS (MSC model). The nomogram had an area under the curve (AUC) of 0.827. For comparison, we also constructed a simplified predictive model including only suture dislodgement, albumin level and BMI (MCS Basic) and an extended model that included all the predictive factors identified from univariate analysis (MCS Extended). These two models had an AUC: 0.790 and AUC: 0.833, respectively. There was no significant difference in performance between the MCS model and the MCS extended models (P = 0.266). Both the MCS model and MCS Extended were significantly better than MCS Basic (P = 0.005 and P = 0.004, respectively). ROC curves for the models are shown in Figure 1. The MCS model was expressed as a nomogram (Figure 2). Nomograms of MCS Extended and models are shown in Supplementary Figures 1 and 2. Clinical utility of the models was compared using DCA. Overall, the MCS

Table 1 Clinicopathological characteristics, *n* (%)

Variable	Non-MCS (*n* = 382)	MCS (*n* = 110)	*P* value
Sex			0.4106
Male	241 (63.1)	64 (58.2)	
Female	141 (36.9)	46 (41.8)	
Age (years)			
< 60	115 (30.1)	35 (31.8)	0.8209
≥ 60	267 (69.9)	75 (68.25)	
Intestinal rapture	14 (3.7)	12 (10.95)	0.0059
Diabetic	89 (23.3)	26 (23.6)	1.0000
Immunotherapy	153 (40.0)	45 (40.9)	0.9592
Neoadjuvant therapy	153 (40.0)	56 (50.9)	0.0548
Suture dislodgement	42 (11.0)	63 (57.3)	< 0.0001
Incision infection	49 (12.8)	42 (38.2)	< 0.0001
BMI (kg/m^2)			
< 24	257 (67.3)	54 (49.1)	0.0007
≥ 24	125 (32.7)	56 (50.9)	
Stoma site			
Ileum	228 (59.7)	83 (75.4)	0.0036
Colon	154 (40.3)	27 (24.6)	
Elevated intra-abdominal pressure	183 (47.9)	65 (59.1)	0.0501
Hemoglobin level			
≤ 90	82 (21.5)	34 (30.9)	0.0501
> 90	300 (78.5)	76 (69.1)	
Albumin level			
≤ 28	54 (14.1)	34 (30.9)	< 0.0001
> 28	328 (85.9)	76 (69.1)	

BMI: Body mass index; MCS: Mucocutaneous separation.

Table 2 Univariate and multivariate analysis

Variable	Univariate, *P* value	Multivariate, *P* value	OR	95%CI	
				Lower	Upper
Suture dislodgement	< 0.0001	< 0.0001	28.0075	11.0901	82.1751
Serum albumin	< 0.0001	0.0008	0.3504	0.1902	0.6485
BMI	0.0006	0.0045	2.1361	1.2660	3.6235
Hemoglobin	0.0409	0.0269	0.5164	0.2881	0.9324
Intestinal rapture	0.0043	0.0351	3.0694	1.0482	8.5558
Incision infection	< 0.0001	0.0179	0.2885	0.0950	0.7624
Neoadjuvant therapy	0.0432	0.0112	1.9769	1.1718	3.3690
Stoma site	0.0028	0.1996	0.6908	0.3881	1.2071
Elevated intra-abdominal pressure	0.0395	0.1194	1.5162	0.2881	0.9324

Diabetic	0.9412	-	-	-	-
Age	0.7309	-	-	-	-
Immunotherapy	0.8717	-	-	-	-
Sex	0.3506	-	-	-	-

BMI: Body mass index.

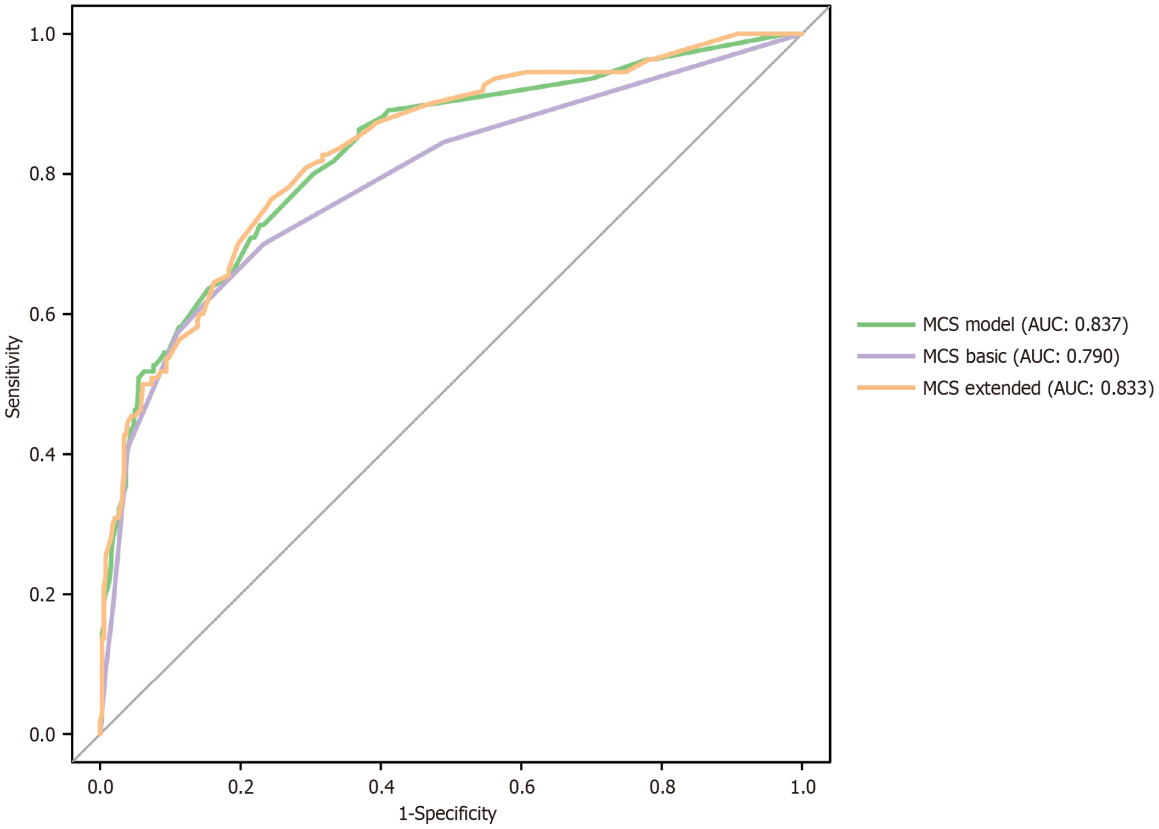

Figure 1 Receiver operating characteristic analysis curves. Mucocutaneous separation (MCS) model is the primary model incorporating all 7 independent predictive factors [suture dislodgment, albumin level, body mass index (BMI), hemoglobin level, intestinal rapture, incision infection and neoadjuvant therapy]. MCS Basic is the stripped-down model using only suture dislodgment, albumin level and BMI. MCS Extended incorporates all the potential predictive factors. MCS: Mucocutaneous separation; AUC: Area under the curve.

model had the best clinical utility compared to the other two models. However, the clinical utility at risk threshold between 0.4 and 0.8 was better in the extended model. Below the risk threshold of 0.4, MSC model and MSC Extended were comparable. Above the 0.8 risk threshold the MCS model was better. DCA analysis results are shown in Figure 3.

DISCUSSION

Enterostomy surgery is commonly used in the treatment of inflammatory bowel dis- ease, intestinal rupture, intestinal obstruction, rectal and anal tumors, and other diseases. Recent studies have shown that high Duke stage, preoperative neoadjuvant chemoradiotherapy, diabetes, inflammatory bowel disease, immunosuppressants, steroids, BMI, albumin levels, and regular follow-up visits by patients are high-risk factors for complications in enterostomy skin. Previous studies have shown that compared to colostomy, patients with ileostomy have higher daily stool output, which is often pasty or watery, carrying various digestive enzymes, making it easy to damage the skin[14].

The results of this study indicate that the risk of MCS in patients with ileostomy is significantly higher than in patients with colostomy. Therefore, for patients with ileostomy who have a large amount of stool output and rapid dissolution of the adhesive base, an enhanced adhesive base should be used, and the ostomy support rod should be removed promptly within one month after surgery. Surgical reasons causing ischemic necrosis of the intestinal mucosa, intraoperative use of electrosurgical devices, and obesity leading to incisional fat liquefaction can all cause skin and mucosal separation[15]. Peristomal fat liquefaction, peristomal abscesses, and infection at the site of enterostomy skin and mucosal sutures

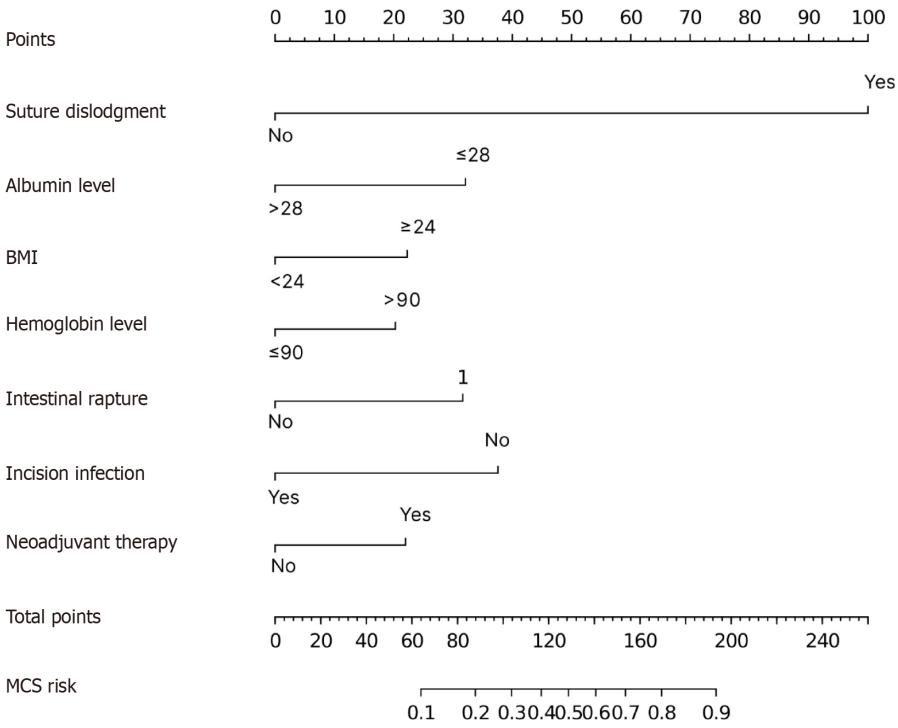

Figure 2 Mucocutaneous separation model nomogram. Visualization of the mucocutaneous separation (MCS) model *via* a nomogram. The risk of MCS is determined based on the total points based on the seven independent predictive variables. MCS: Mucocutaneous separation.

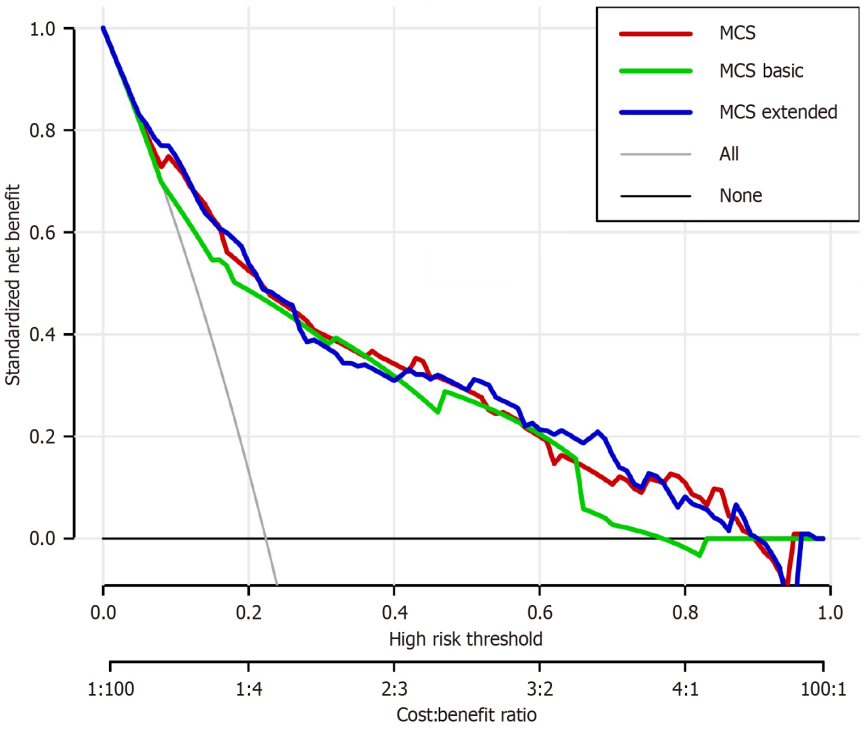

Figure 3 Decision curve analysis. The clinical utility of the three models is generally comparable, however, at higher risk profiles, the mucocutaneous separation model is generally better. MCS: Mucocutaneous separation.

significantly increase the probability of MCS[16]. The results of this study show that partial necrosis of the enterostomy intestinal mucosa, detachment of enterostomy mucosal sutures, subcutaneous fluid infection around the enterostomy, liquefaction of local tissue around the enterostomy, and incision infection all increase the risk of MCS. It is recommended that when patients have symptoms of infection, secretions from the wound should be collected for bacterial culture, and antibiotic treatment should be administered according to the doctor's orders. With good intestinal function, solid food intake should be increased to prevent fecal contamination of the wound. Physicians should remove ineffective sutures at

the site of MCS, and clean and remove necrotic tissue from the wound.

When the enterostomy roll edge leaks or becomes pale, it should be replaced promptly to prevent fecal leakage and delay wound healing. When serum albumin levels are < 35 g/L, the risk of postoperative site infection will increase by 2.5-fold[17]. Another study found that preoperative low albumin levels are independent risk factors for deep skin and mucosal separation[18]. Multiple studies have shown that patients in a malnourished state have low immune function and should receive enteral or parenteral nutrition support before and after surgery to improve immune function and effectively prevent skin and mucosal separation[19,20]. The results of this study indicate that when serum albumin levels are low, indicating malnutrition, the probability of MCS occurrence significantly increases. Poor nutritional status in patients is a high-risk factor for MCS occurrence. It is recommended to strengthen patient health education, provide dietary guidance to patients, and enhance patient awareness of nutritional supplementation and dietary balance.

This study was based on a prospective design, employing uniform criteria to identify the occurrence of MCS, and to avoid subjective bias, outcome assessment was conducted blindly. Additionally, predictive variables were rigorously selected by an expert team following relevant guidelines[21]. Through extensive literature review, expert consultations, and preliminary investigations, predictive factor variables were selected. Single-factor analysis and multi-factor analysis were conducted to obtain the strongest combination of variables for joint prediction. Furthermore, the measurement methods for the included predictive variables were simple, data acquisition was relatively convenient, and the model exhibited good reproducibility and operability. In addition to these findings, the potential of Negative Pressure Wound Therapy (NPWT) as a treatment for complicated cases of MCS is noteworthy. A recent case series by Ding *et al*[22] demonstrated the effectiveness of NPWT in managing moderate to severe MCS following ileal conduit urinary diversion. Their study showed that NPWT not only prevented infection but also facilitated the healing process in patients with significant MCS. This suggests that NPWT could be considered a therapeutic option in severe cases of MCS, particularly where conventional treatments may be insufficient. Future studies should explore the broader applicability of NPWT in MCS management following enterostomy surgery.

While this study offers valuable insights into the risk factors and predictive model for MCS in enterostomy patients, several limitations should be acknowledged. Firstly, as a single-center study, the findings may not be generalizable to other populations or settings, where different surgical techniques, postoperative care protocols, and patient demographics may influence the incidence and risk factors of MCS. Additionally, although the study employed a prospective design and rigorous criteria for identifying MCS, the potential for selection bias remains, as patients who were critically ill, deceased, or lost to follow-up were excluded from the analysis. Moreover, the reliance on expert assessment for determining MCS may introduce some level of subjectivity, despite the blinding procedures used. Lastly, while the model demonstrated good predictive accuracy, external validation in diverse clinical settings is necessary to confirm its broader applicability. Future studies should also explore the inclusion of additional variables, such as genetic predispositions and long-term patient outcomes, to enhance the robustness of the model.

CONCLUSION

MCS often occurs within 1 to 3 weeks after enterostomy surgery. If MCS is not promptly addressed, it can lead to complications such as irritant dermatitis, stoma retraction, stoma stenosis, and even stoma reconstruction, which can significantly increase the psychological and economic burden on patients and their families, causing immense suffering. The MCS risk prediction model developed in this study demonstrates good predictive performance, providing a scientific basis for early warning and precise prevention of MCS complications. It can guide the development of MCS prevention and intervention strategies. However, this study has certain limitations. It only underwent temporal validation, and the number of modeling samples needs to be further increased. The external validity of this model needs to be verified in different hospitals.

FOOTNOTES

Author contributions: Liu Y and Ye JH contributed to conceptualization; Liu Y contributed to methodology; Li H contributed to writing—original draft preparation; Wu JJ and Ye JH contributed to writing—review and editing; contributed to supervision; All authors have read and agreed to the published version of the manuscript.

Supported by the Zhejiang Province Medical and Health Science and Technology Plan Project, No. 2022KY1427.

Institutional review board statement: This study was approved by the Ethics Committee of Zhejiang University of Traditional Chinese Medicine Teaching Hospital, Lishui Central Hospital. The study was conducted in line with the Helsinki Declaration.

Informed consent statement: All study participants, or their legal guardians, provided written consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Underlying data is restricted by patient privacy restrictions. Data requests may be made to the corresponding author.

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.

Country of origin: China

ORCID number: Jian-Hong Ye 0009-0002-3035-2114.

S-Editor: Liu JH
L-Editor: Webster JR
P-Editor: Zhang L

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6629-6634

DOI: 10.12998/wjcc.v12.i33.6629

ISSN 2307-8960 (online)

CASE REPORT

Infection with *Listeria monocytogenes* meningoencephalitis: A case report

Da-Zhen Xu, Quan-Hui Tan

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B
Novelty: Grade A
Creativity or Innovation: Grade A
Scientific Significance: Grade B

P-Reviewer: Lin FJ

Received: May 1, 2024
Revised: September 5, 2024
Accepted: September 9, 2024
Published online: November 26, 2024
Processing time: 148 Days and 20.4 Hours

Da-Zhen Xu, Department of Nursing, Shanghai Sixth People's Hospital, Shanghai 200233, China

Quan-Hui Tan, Department of Infectious Disease, Shanghai Sixth People's Hospital, Shanghai 200233, China

Corresponding author: Quan-Hui Tan, PhD, Academic Research, Department of Infectious Disease, Shanghai Sixth People's Hospital, No. 600 Yishan Road, Xuhui District, Shanghai 200233, China. tanquanhui@sina.cn

Abstract

BACKGROUND

Listeria meningitis is an infectious disease of the central nervous system caused by *Listeria monocytogenes*. This bacterium is widely present in the natural environment and can be transmitted through channels such as food and water. Patients usually show symptoms such as fever, headache, and neck stiffness. In severe cases, coma, convulsions, or even death may occur. Traditional diagnostic methods, such as cerebrospinal fluid (CSF) culture and serological tests, have certain limitations. Although CSF culture is the "gold standard" for diagnosis, it is time-consuming and has a relatively low positivity rate. Serological detection may also result in false positive or false negative results. The emergence of metagenomic sequencing (mNGS) technology has led to a significant break-through in diagnosing Listeria meningitis, allowing quick and accurate detection of various pathogens in samples.

CASE SUMMARY

Here, we present the case of a previously healthy 64-year-old woman diagnosed with Listeria meningitis using mNGS. She was successfully treated with intravenous ampicillin and meropenem, without any complications.

CONCLUSION

Listeria meningitis must be considered, especially in patients who fail to show improvement with first-line antibiotic treatments. mNGS significantly reduces the diagnosis time, supporting timely treatment of patients.

Key Words: *Listeria monocytogenes*; Meningitis; Diagnosis; Treatment; Immune function; Case report

Core Tip: Listeria meningitis is a potentially serious condition with a high associated mortality rate, making its early diagnosis crucial. In immunocompromised patients, active administration of first-line antibiotics can help achieve better clinical outcomes.

Citation: Xu DZ, Tan QH. Infection with *Listeria monocytogenes* meningoencephalitis: A case report. *World J Clin Cases* 2024; 12(33): 6629-6634
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6629.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6629

INTRODUCTION

Listeria monocytogenes (LM) is a facultative anaerobic bacterium that causes Listeria meningitis[1]. LM is an intracellular, parasitic, Gram-positive, non-spore-forming bacillus and a zoonotic pathogen[2]. This bacterium is widely present in natural environments such as soil and water, and has a strong tolerance to low temperatures and high salinity[3]. It is a foodborne bacterium that easily contaminates various foods such as dairy products, seafood, meat and eggs, poultry, fruits, and vegetables. It is widely present in refrigerated foods and is classified as an opportunistic pathogen[4]. Patients often have a history of catching a cold and directly consuming refrigerated food before the onset of the disease. Susceptible populations include newborns, pregnant women, the elderly, and individuals with low immunity[5]. After consuming food contaminated with LM, the bacteria enter intestinal epithelial cells by binding to the adhesive proteins on the surface of the cells, multiply within the cells, and use actin to spread between cells, thereby passing through the intestinal barrier and the blood-brain barrier and spreading to any part of the body[6].

LM meningitis usually has an acute onset. The first symptom in 90% of cases is fever, often exceeding 39 °C and accompanied by severe headaches, dizziness, nausea, and vomiting. There is obvious meningeal irritation, and patients often exhibit altered consciousness, including numbness, delirium, and seizures. In severe cases, loss of consciousness may occur within 24-48 h[7]. A few cases have a slow onset, a long disease course, and repeated episodes. If the lesion involves the brain parenchyma, symptoms of encephalitis or brain abscess may develop[8]. Some patients may experience double vision, difficulty in pronunciation or swallowing, facial nerve paralysis, and hemiplegia. Cerebrospinal fluid (CSF) examination typically reveals a cloudy appearance, increased WBC count and multinucleated cell count, elevated protein levels, and reduced sugar and chloride concentrations[9]. LM can also be found in blood and CSF cultures. LM is sensitive to penicillin, ampicillin, gentamicin, streptomycin, chloramphenicol, quinolones, rifampin, and sulfamethoxazole/trimethoprim, among others. Penicillin or ampicillin are the primary therapeutic drugs, although they do not show bactericidal effects *in vitro*. In severe cases, these two antibiotics are often used in combination. The combination of ampicillin or penicillin with aminoglycoside antibiotics has a synergistic effect. The clinical manifestations and CSF findings in LM meningitis are not significantly different from those of other forms of suppurative meningitis, making its diagnosis and treatment challenging for clinicians. This requires careful clinical attention. Our department has successfully treated a critically ill patient with LM meningitis. The diagnosis and treatment process are reported below.

CASE PRESENTATION

Chief complaints

Intermittent fever and headache for 1 month and convulsions and confusion for 2 days.

History of present illness

On May 8, 2021, the patient developed a fever for no apparent reason, with a maximum body temperature of 39.3 °C, accompanied by headache and forceful vomiting, without any loss of consciousness or convulsions.

History of past illness

The patient had a history of systemic lupus erythematosus (SLE) for more than 10 years. During the 6 months when she was abroad, she had stopped taking steroids on her own. Upon returning to China 2 months prior to admission, she underwent a comprehensive examination in the nephrology department, followed by a re-examination that showed decreased complement C3 and C4 levels. Three doses of methylprednisolone had been administered orally to control her SLE.

Personal and family history

All members of her family were in good health and had no history of tuberculosis or other related diseases.

Physical examination

The patient's body temperature was 38.9 °C, heart rate was 137 beats/min, respiratory rate was 26 times/min, and blood pressure was 155/81 mmHg. She was in a deep coma, with pupils that were equal, round, reactive to light, and measured 3 mm bilaterally. Neck stiffness was noted. Slightly thick breathing sounds were observed in both lungs, but no dry or wet rales were heard. The heart rate was 137 beats/min, regular, with no pathological murmur. The abdomen was flat and soft, and the liver, spleen, and ribs were unaffected. The left upper limb was ankylosed, and there was no edema in both lower limbs. No pathological reflex was elicited.

Laboratory examinations

Blood tests revealed a rapid c-reactive protein level of 31.65 mg/L, a WBC count of 5.5 × 10^9/L, and a neutrophil percentage of 90.9%. The CSF pressure was 250 mmH_2O, total WBC count was increased, protein levels were significantly increased, and glucose and chlorine levels were decreased.

On the 4th day of admission, mNGS of the CSF indicated the presence of LM (Table 1), and both blood and CSF cultures were positive for LM. Serum complement C3 and C4 levels were normal. Other diagnostic tests, such as the T-cell spot of tuberculosis test (T-SPOT), CSF latex agglutination test, CSF tuberculosis (TB)-PCR, and autoimmune brain antibody tests were all negative.

Imaging examinations

Electroencephalography: Display exception.

Head magnetic resonance imaging: Multiple small ischemic lesions in the bilateral frontal, parietal, temporal, and occipital lobes, as well as the lateral ventricles.

Chest computed tomography revealed local callus formation after fractures of the right fourth to ninth ribs. In addition, a review of electroencephalography showed abnormalities, with irregularities on the video electroencephalography topographic map. Head CT and MRI showed scattered small ischemic foci in the bilateral frontal and parietal lobes, basal ganglia, and lateral ventricles.

MULTIDISCIPLINARY EXPERT CONSULTATION

After admission, the patient received electrocardiographic monitoring, oxygen therapy, and critical illness reporting. A lumbar puncture was performed, revealing CSF pressure of 250 mmH_2O, an increased total WBC count, significantly increased protein levels, and decreased glucose and chlorine levels (Table 2). Central nervous system (CNS) infections (excluding bacteria, tuberculosis, fungi, and viruses) and lupus encephalopathy were considered possible diagnoses. Samples were sent for three smears (bacterial, fungal, and acid-fast staining), three cultures, latex agglutination tests, TB-PCR, CSF mNGS, autoimmune brain antibodies, and blood T-SPOT tests, with consultation from the Department of Rheumatology and Immunology. The patient was treated with anti-infection therapy (1.0 g q8h of meropenem + 0.5 g qd of ribavirin), dehydration treatment to reduce intracranial pressure (125 mL q8h of 20% mannitol + 250 mL of glycerol fructose q12h), diagnostic anti-tuberculosis treatment (0.3 g qd of isoniazid, 0.45 g of rifampin, 0.75 g of ethambutol, and 0.5 g of pyrazinamide; all *via* nasal feeding), 500 mg × 3 days of methylprednisolone intravenous infusion, 20 g × 5 days of intravenous immunoglobulin therapy, and control of epileptic seizures (diazepam and levetiracetam).

FINAL DIAGNOSIS

Infection with LM meningoencephalitis and SLE.

TREATMENT

On the 4th day of admission, mNGS of the CSF indicated LM (Table 1), and the blood and CSF cultures also tested positive for LM. Serum complement C3 and C4 levels were normal, and tests for T-SPOT, CSF latex agglutination, CSF TB-PCR, and autoimmune brain antibodies were all negative. The diagnostic evidence for tuberculous meningitis, cryptococcal meningitis, lupus activity, and lupus encephalopathy was insufficient, and the diagnosis was finally confirmed as sepsis caused by LM and LM meningoencephalitis. Therefore, the anti-tuberculosis drugs were discontinued, and the anti-infective regimen was adjusted to meropenem 2 g q8h + ampicillin 3 g q6h *via* intravenous infusion. The methylprednisolone dosage was reduced to 3 capsules qd *via* nasal feeding. Antiepileptic treatment, dehydration treatment to reduce intracranial pressure (125 mL q6h mannitol + 250 mL q12h glycerol fructose intravenous infusion), and symptomatic supportive treatment were continued.

Table 1 Metagenomic sequencing results of cerebrospinal fluid

Name	Number of detected sequences	Gene percentage	Copies/mL
Listeria monocytogenes	1317	195077 bp/6.34%	9.90^{E+02}

Table 2 Results of cerebrospinal fluid examination during hospitalization

Cerebrospinal fluid (reference interval)	Day 1	Day 7	Day 14	Day 30
Pressure (80-180 H_2O)	210	150	100	80
Color (transparent and clear)	Primrose	Colorless transparent	Colorless transparent	Colorless transparent
Leucocyte (0-8 × 10^6/L)	75	18	5	1
Erythrocyte (10^6/L)	110	7	5	3
Lymphocyte	16	90	3	1
Neutrophils	82	8	1	0.5
Macrophage	1	2	0	0
Eosinophilic granulocyte	1	0	0	0
Basophilic granulocyte	0	0	0	0
Sugar mmol/L	3	2.53	2.79	4.1
Chlorine	123	131	125	130
Protein	3.32	1.16	0.66	0
Bacterial culture	*Listeria monocytogenes*	Negative	Negative	Negative

OUTCOME AND FOLLOW-UP

The patient's consciousness gradually improved, and cognitive functions, such as the ability to calculate, gradually recovered. She could follow instructions and perform simple movements, and her body temperature remained normal. Repeated blood and CSF cultures showed no bacterial growth, and her condition improved. On July 24, the patient was discharged to a rehabilitation hospital for further rehabilitation treatment. During the treatment period in this hospital, lumbar punctures were re-examined in the 1st and 2nd weeks after admission. The biochemical and routine CSF findings were normal, and the CSF culture was negative. The patient experienced no fever, had clear consciousness, and was able to care for herself. She was considered clinically cured.

DISCUSSION

Infections of the CNS are still associated with high morbidity and even mortality[10]. LM belongs to the group of bacteria that have a specific potential to invade and access the CNS, mainly causing meningitis and rhombencephalitis. Neurolisteriosis typically affects immunocompromised individuals but can also occur in immunocompetent patients[11]. Particularly vulnerable populations include pregnant women, unborn babies, newborns, and the elderly[12]. The mechanisms by which LM invades the CNS and its associated tropism toward neural tissues are still poorly understood[13]. Since LM is mostly acquired orally through the ingestion of contaminated food, it seems apparent that the bacterium can be transported by the trigeminal nerve to the brainstem, resulting in LM-induced rhombencephalitis[14]. This pathology has been observed in more than 200 cases of neuropathological investigations in cattle, sheep, and goats, and in autopsies of patients who died from LM brainstem encephalitis[15-16]. These investigations revealed inflammation and infiltration of cranial nerves and their pathways[17-18].

The patient in this case was an elderly woman with weakened immune function owing to a history of SLE and prolonged hormone therapy, which she had recently discontinued. The onset of the disease was characterized by fever, headache, and neurological symptoms, such as altered consciousness and epileptic seizures. These symptoms, along with brain parenchymal damage, neck stiffness, and ischemic lesions on head CT and MRI, raised concerns of CNS infection, although lupus encephalopathy could not be ruled out. After admission, a complete lumbar puncture was performed as soon as possible, and routine CSF analysis, biochemical tests, smear and culture, mNGS, cryptococcal latex agglutination test, TB-PCR, and autoimmune brain antibody tests were conducted. Based on the patient's medical history and CSF findings, tuberculosis, bacterial, fungal meningitis, and lupus encephalopathy could not be ruled out. The patient's condition was critical and was progressing rapidly. Without timely and active treatment, there was a high risk of life-threatening conditions such as continuous epilepsy, respiratory failure, or brain herniation. Therefore, before determining

the cause of the infection, a broad treatment approach was initiated to take into account bacterial infections, tuberculosis, and lupus encephalopathy. Active antibacterial treatment, diagnostic anti-tuberculosis therapy, high-dose hormone shock, and immunoglobulin therapy were given. Through tests such as serum complement, T-SPOT, CSF latex agglutination, CSF TB-PCR, autoimmune brain antibodies, CSF mNGS, and both CSF and blood cultures, a final diagnosis of LM meningoencephalitis was confirmed. The treatment plan was adjusted as follows: High-dose hormones and anti-tuberculosis drugs were stopped and replaced by low-dose hormone maintenance. The patient was treated with meropenem 2 g q8h, ampicillin 3 g q6h, and measured to reduce dehydration to reduce intracranial pressure. Nutritional support was also provided, which gradually improved her condition.

In the treatment of patients with CNS infections, it is necessary to closely observe changes in the patient's body temperature, consciousness, breathing, pupil response, and blood gas levels. In case of brain herniation or respiratory failure, it is necessary to reduce intracranial pressure promptly, along with the provision of tracheal intubation and assisted ventilation *via* a ventilator to save the patient's life. During the treatment process, attention should be paid to maintaining airway patency, preventing phlegm obstruction, and strengthening nursing and nutritional support.

In addition, the patient had a history of untreated SLE, complicating the diagnosis. It was necessary to distinguish between SLE encephalopathy and secondary CNS infection related to SLE, as there are significant differences in the treatment methods for these two conditions. SLE encephalopathy typically requires high-dose hormone shock therapy, whereas CNS infections require timely and effective anti-infective drug treatment. However, the use of high-dose hormones in cases of infection may exacerbate the spread of infection, making it more difficult to control.

Identifying the pathogen is an important aspect of the diagnosis and treatment of infectious diseases. In this case, the patient's CSF routine and biochemical manifestations were atypical, which made it difficult to identify the type of pathogen. Therefore, after admission, in addition to routine blood and CSF cultures, the patient underwent a CSF mNGS examination as soon as possible. This quickly and accurately detected LM, which was later confirmed by blood and CSF cultures. Multi-disciplinary consultations and a thorough examination of SLE-related indicators helped rule out other CNS diseases such as SLE encephalopathy, autoimmune encephalitis, and cerebrovascular disease.

CONCLUSION

Listeria meningitis is an infectious disease of the CNS caused by LM, a bacterium widely present in the natural environment and transmitted through contaminated food and water sources. Patients usually show symptoms such as fever, headache, and neck stiffness. In severe cases, coma, convulsions, or even death may occur. Traditional diagnostic methods include CSF culture, serological detection, *etc.*, but these methods have certain limitations. Although CSF culture is the "gold standard" for diagnosis, it is time-consuming and has a relatively low positivity rate. Serological detection may result in false positive or false negative results, further complicating the diagnosis.

The emergence of mNGS technology has revolutionized the diagnosis of LM. It can quickly and accurately detect various pathogens in samples, including bacteria, viruses, and fungi. It offers several significant advantages over traditional methods. First, it is fast and accurate. mNGS can analyze a large number of nucleic acid sequences in a short time and quickly determine the pathogen species in the sample. Compared with traditional CSF culture, mNGS can greatly shorten the diagnosis time and provide strong support for the timely treatment of patients. Second, it has high sensitivity and specificity. It can detect pathogen nucleic acids at extremely low concentrations, improving diagnostic sensitivity. Moreover, it distinguishes between different pathogens through precise analysis of nucleic acid sequences, improving diagnostic specificity. In some complex cases, there may be infections caused by rare pathogens or mixed infections. Traditional diagnostic methods often struggle to identify such infections, whereas mNGS can comprehensively detect various pathogens in samples and provide more information for accurate diagnosis.

FOOTNOTES

Author contributions: Xu DZ and Tan QH jointly collected the data and co-authored this paper. Both authors have read and approved the final version of the manuscript for publication.

Supported by National Natural Science Foundation of China, No. 82100631.

Informed consent statement: Informed consent for the publication of this article was obtained from the patient.

Conflict-of-interest statement: None of the authors have any conflict of interest to declare.

CARE Checklist (2016) statement: We have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country of origin: China

ORCID number: Quan-Hui Tan 0000-0002-6314-5835.

S-Editor: Luo ML
L-Editor: Filipodia
P-Editor: Cai YX

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6635-6643

DOI: 10.12998/wjcc.v12.i33.6635

ISSN 2307-8960 (online)

CASE REPORT

Platelet-rich plasma treatment for chronic wounds: A case report and literature review

Ana Dimova, Martin Boroš, Stefan Dimov, Janja Konjevod, Maja Svetec

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade D

Creativity or Innovation: Grade D

Scientific Significance: Grade C

P-Reviewer: Mok P

Received: June 30, 2024

Revised: August 17, 2024

Accepted: September 2, 2024

Published online: November 26, 2024

Processing time: 88 Days and 6.5 Hours

Ana Dimova, Martin Boroš, Stefan Dimov, Janja Konjevod, Department of Surgery, Zabok General Hospital and the Croatian Veterans Hospital, Zabok 49210, Croatia

Ana Dimova, Stefan Dimov, Department of Surgery, St Catherine Specialty Hospital, Zagreb 10000, Croatia

Maja Svetec, Department of Emergency Medicine, Zabok General Hospital and the Croatian Veterans Hospital, Zabok 49210, Croatia

Corresponding author: Ana Dimova, MD, Surgeon, Department of Surgery, Zabok General Hospital and the Croatian Veterans Hospital, Bračak 8, Zabok 49210, Croatia. ana.dimova@svkatarina.hr

Abstract

BACKGROUND

Wound healing is a complicated process that can be heavily influenced by patient comorbidities, in some cases leading to a chronic non-healing wound. Evidence presented in the medical literature supporting the clinical use of autologous platelet-rich plasma (PRP) in treatment of such wounds is becoming increasingly compelling. Mechanisms involved include complex interactions between the patient's thrombocytes, cytokines, and growth factors.

CASE SUMMARY

We present a case of a 72-year-old male patient with a long-standing chronic wound and multiple comorbidities. Over the course of more than 7 months, the patient was unsuccessfully treated with all routinely used measures, including different dressing approaches. Multiple antibiotic regimens were administered for wound infection, with repeated evaluation of microbiological swab results. Finally, after three PRP applications, the wound showed clinical improvement with complete restitution of the epithelial layer of the skin.

CONCLUSION

PRP treatment may be beneficial to reduce healing time in chronic wounds.

Key Words: Wound healing; Platelet-rich plasma; Growth factors; Antibiotics; Wound Infection; Case report

Core Tip: Chronic wounds present a huge burden on healthcare systems worldwide, and diminish the quality of life of affected patients tremendously. Chronic wounds are often a source of frustration for attending clinicians as well, since many different types of dressings and other forms of conservative therapy and surgical debridement are used. We believe that local platelet-rich plasma (PRP) application is an easily performed procedure that could be offered to patients with chronic wounds after the failure of standard dressing-type procedures. We also believe that other more invasive regenerative treatment options should be postponed until after PRP is attempted.

Citation: Dimova A, Boroš M, Dimov S, Konjevod J, Svetec M. Platelet-rich plasma treatment for chronic wounds: A case report and literature review. *World J Clin Cases* 2024; 12(33): 6635-6643
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6635.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6635

INTRODUCTION

A chronic wound is defined as a skin barrier defect that persists after 3 months of the wound being sustained. This represents a major therapeutic challenge faced in clinic and is common among older patients with obesity, diabetes mellitus, and vascular disorders. Tissue repair is a universal phenomenon across all multicellular organisms, and much of the insight about mechanisms of wound healing and the relative temporal progression of the healing phases has come from studies in mice[1,2]. Deviation from the normal physiological healing process may be due to various factors, such as poor blood supply, impaired immune function, or inadequate nutritional support. Chronic wounds can cause significant distress to patients and place a heavy burden on the medical system[3].

Platelet-rich plasma (PRP) is an autologous blood-derived product containing high thrombocyte concentrations and various platelet-related growth factors; the thrombocyte levels of such are often 2-5 times higher than in normal blood. The utilization of these plasma products was first described by hematologists in the 1960s and 1970s, and they have since been used in various surgical and non-surgical fields such as dermatology, sports medicine, and orthopedics[4,5]. Recent systematic reviews and meta-analyses of randomized controlled trials have demonstrated that autologous PRP therapy effectively enhances wound healing and is considered a viable biological adjuvant therapy option in patients with non-healing diabetic foot ulcers[6].

Alpha-granules present in thrombocytes contain an abundance of growth factors, such as transforming growth factor β 1 (TGF-β1), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor 1, platelet-derived growth factor (PDGF), and fibroblast growth factor, all of which play valuable roles in the mechanisms of healing. Upon their release from the alpha-granules, polypeptides and their receptors are activated to promote wound closure, which is achieved through cell differentiation and proliferation, chemotaxis, collagen synthesis, and angiogenesis. The PRP itself promotes wound healing due to the increased concentrations of these factors[7,8].

Older adults are more prone to chronic wounds than their younger counterparts, although both suffer significant impact to their quality of life from such. The true prevalence and incidence are hard to distinguish due to a lack of standardization in data collection. A substantial number of chronic wounds are underreported or not accurately described, especially when studies focus on other endpoints, such as lower-extremity amputations. It is also difficult to predict and identify prognostic factors for wound healing because of the multifactorial pathogenesis and different wound etiologies[9].

Patients with diabetes mellitus have impaired healing capabilities and run the risk of prolonged wound healing. Between 1 in 3 to 1 in every 5 patients with diabetes mellitus will develop a chronic non-healing wound in their lifetime. Non-diabetic patients have better regulation of angiogenesis and local inflammatory response to wound healing, as well as a more effective immune response to colonizing bacteria, with lower levels of reactive oxygen species[10]. Even when chronic wounds in diabetic patients heal, there is a risk of recurrence. The risk of recurrence within 1 year is roughly 40%, although it can be as high as 65% within 5 years. Some risk factors for diabetic ulcer recurrence have been identified, such as those involving progression of neuropathy, wound infection, peripheral artery disease, pre-ulcerative lesions, glycated hemoglobin level above 7.5%, and social factors[11].

Herein, we present the case of a patient with a long-standing chronic wound and multiple comorbidities, who was unsuccessfully treated with all routinely used measures, including different dressing approaches. Multiple antibiotic regimens were administered for wound infection, with repeated evaluation of microbiological swab results. Finally, after three PRP applications, the wound showed clinical improvement with complete restitution of the epithelial layer of the skin.

CASE PRESENTATION

Chief complaints

A 72-year-old male patient was admitted to our emergency department after suffering a contusion and superficial skin excoriation of the right lower leg from a wood log impact. His recovery was complicated by the development of a large

hematoma that mandated incision and drainage. Eventually, a chronic wound developed at the incision site and persisted for 7.5 months.

History of present illness

Upon admission to our emergency department, the wound was cleaned and dressed. According to national guidelines and the patient's antitetanic immunization status, combined active-passive immunization with tetanus toxoid and 50 U of human tetanus immunoglobulin was administered. Dual antibiotic first-line oral therapy was prescribed for 10 days in dosages of amoxicillin and clavulanic acid at 875 mg + 125 mg, twice daily, and clindamycin at 600 mg, three times daily.

History of past illness

The patient's general health status was burdened with several comorbidities, including arterial hypertension, atrial fibrillation, type 2 diabetes mellitus, mitral regurgitation, and a cerebrovascular accident.

Personal and family history

The patient's personal and family history did not contain any significant events.

Physical examination

At presentation, the patient had localized swelling and a large area of superficial anterior lower leg skin excoriation, measuring 20 cm × 10 cm. Warfarin was temporarily discontinued from his longstanding therapy and replaced with low-molecular-weight heparin treatment in a dosage of 6000 IU daily, administered subcutaneously. However, 4 days after the traumatic incident, despite the exclusion of warfarin, the patient developed an inflamed hematoma measuring 10 cm × 7 cm.

Laboratory examinations

After the patient developed the inflamed hematoma, laboratory tests revealed C-reactive protein (CRP) levels rising to 71.5 mg/L (normal range: 0.0–5.0 mg/L) and a leukocyte level of 9.1 × 10^9/L (normal range: 3.4–9.7 × 10^9/L), with a neutrophil relative count of 75.2% indicating a leftward shift. Incision and drainage of the hematoma was performed, with necrectomy of three separate marked areas of skin necrosis measuring 3 cm × 3 cm.

The patient was admitted to the hospital for intravenous antibiotic treatment of amoxicillin and clavulanic acid in dosages of 1 g + 200 mg, three times a day, and metronidazole at 500 mg, three times a day. Regular wound cleaning and dressing was performed daily, as well as addressing the possible signs of compartment syndrome. Due to lack of clinical response to the administered antibiotics (evidenced by persistent erythema and swelling with mild induration and CRP levels rising up to 161.0 mg/L, with leukocytes of 7.6 × 10^9/L and neutrophils making up 74.0% of white blood cells), on the 3rd day of hospitalization the amoxicillin was replaced with intravenous clindamycin in a dosage of 600 mg, three times daily, which led to clinical improvement.

Three days after the antibiotic replacement, a regression of local inflammation signs was observed and CRP levels dropped to 86.9 mg/L, with the leukocyte level lowering to 5.5 × 10^9/L and the relative neutrophil count to 68.1%.

Imaging examinations

Initial X-ray examinations revealed no fractures or other pathologies, apart from demineralization of the tibia and calcifications in the arteries of that region.

Further diagnostic work-up

The patient was discharged on day 6 after hospitalization in good general condition, afebrile, and without signs of compartment syndrome. Satisfying local healing dynamics were seen, with an erythema regression observed in the proximal and distal part of the wound. Oral antibiotic therapy was continued for 7 days with clindamycin at 600 mg, three times daily, and metronidazole at 400 mg, three times daily. The patient's right lower leg was cast-immobilized. The immobilization was removed at a surgical check-up appointment 2 weeks later.

After this first hospitalization, the wound healing progressed in an uneventful manner; the patient was asymptomatic over this 30-day period, recorded at three consequent follow-up appointments in the outpatient department. However, at 1 month after he had been discharged from the hospital, a markedly increased secretion was noted from the wound, along with erythema and induration of the lower leg. A microbiological swab was taken and an immobilization casting of the right lower leg was performed again. The patient was admitted to hospital for the second time because of the cellulitis that had developed. In addition, low-molecular-weight heparin treatment was again introduced to replace warfarin. Wound swabs after 3 days showed methicillin-resistant *Streptococcus aureus* (MRSA) and *Klebsiella pneumoniae* (extended-spectrum β-lactamases); sensitivity testing showed both to be responsive to sulfamethoxazole and trimethoprim treatment, and the combination antibacterial therapy was started immediately. The patient was discharged after 5 days, with continuation of the oral sulfamethoxazole and trimethoprim antibiotic treatment in dosages of 400 mg + 80 mg, twice daily, for 10 days.

During the next month, the wound healed by secondary intention, with several necrectomies required due to necrotic demarcation of the edges of the wound. Regular follow-up visits to the outpatient department with wound care took place every 7-14 days, with primary care visits every 2-3 days. During this treatment phase, the wound reduced in size, there was no induration or erythema, and wound secretion was minimal. Unfortunately, the reduction of wound size eventually stopped, leaving the patient with a chronic wound measuring 18 cm × 3 cm to 18 cm × 4 cm. Furthermore, 3 months after the incision and hematoma drainage, hypergranulation tissue was noted on the wound edges, and the

patient started complaining of heavy pain in the wound area.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient complained of persistent pain 6 months after the initial trauma. At that point, the wound was 15 cm long with redness along its boundaries, but without secretion and fluctuation. Oral clindamycin antibiotic treatment was given three times daily in doses of 600 mg for 2 weeks.

In a follow-up appointment we noted no success and persistent erythema measuring 12 cm × 2 cm to 12 cm × 3 cm. Due to the lack of clinical response to the oral antibiotic regimen, the patient was readmitted to hospital for the third time. New swab results were reviewed by an infectologist to address the presence of multidrug-resistant organisms. Isolates of MRSA and *Enterobacter spp* had been found in the wound swabs, and the infectologist indicated application of oral sulfamethoxazole and trimethoprim in dosages of 800 mg + 160 mg, twice daily, and intravenous application of meropenem in a dosage of 1 g, daily. The wound infection subsided in response to this treatment regimen. The patient was discharged after 5 days with oral antibiotic sulfamethoxazole and trimethoprim treatment in a dosage of 800 mg + 160 mg, twice daily, for 7 more days.

FINAL DIAGNOSIS

The patient was ultimately diagnosed with a chronic wound of the right lower leg.

TREATMENT

Seven and a half months after the initial trauma, microbiological swabs revealed physiological flora in a chronic wound measuring 12 cm × 3 cm with moderate-to-heavy persistent pain [visual analog scale (VAS), 6–8]. Hyperbaric oxygen treatment was considered; however, as the patient could not get an appointment within 3 months and due to the patient's poor compliance to such a scenario, we opted for PRP treatment to promote wound healing and relieve his chronic pain.

A multidisciplinary consultation between the specialists involved in treatment concluded that PRP injection should not be administered if the swab results showed pathological microorganisms or anything except physiological flora. Also, the patient needed to be hemodynamically stable, without other acute illnesses and with adequate laboratory values of red blood cells and thrombocytes, which were within normal range for our patient. These requirements were met and we began the PRP treatment protocol.

Autologous PRP was obtained by venipuncture and aspiration of 15 mL of the patient's peripheral venous blood using the Arthrex ACP® Double-Syringe System (Naples, FL, United States). The test tube was then centrifuged at 1,500 rpm for 5 minutes (Horizon 24-AH centrifuge; Drucker Diagnostics, Port Matilda, PA, United States). From the separated plasma, we obtained 6 mL of PRP to be used for application *via* the Double-Syringe System (Figure 1). Autologous PRP (4 mL) was then administered around the wound edges, and the remaining PRP (2 mL) was freely sprayed onto the wound surface. Wound aftercare was performed every 2nd day with application of 0.9% NaCl and a sterile cotton mesh covering.

The patient showed markedly positive results with regard to VAS score diminution to 3–4 as early as 2 days post-procedurally. Two weeks after the first PRP application, improved healing was observed. The patient received a second and third PRP application in the same manner, at a day-hospital, with 2-week interval. Further improvement, both subjective and objective, was observed, and 4 weeks after the third PRP application we decided to cancel the further planned PRP applications due to the patient's complete lack of pain and the observed complete restitution of skin integrity. Wound images taken immediately before the application of autologous PRP and after three PRP treatments show the tremendous improvement (Figure 2).

OUTCOME AND FOLLOW-UP

Six months after the third PRP application, the patient was still fully mobile, free of pain, and returned to his normal activities, with no residual skin defects (Figures 3 and 4). He reported no pain and complete quality of life and mobility restitution.

DISCUSSION

Chronic wounds with poor response to conventional wound dressings and treatments are a relatively common healthcare problem and can pose a real clinical challenge. Autologous PRP treatment could impact the costs in chronic wound management.

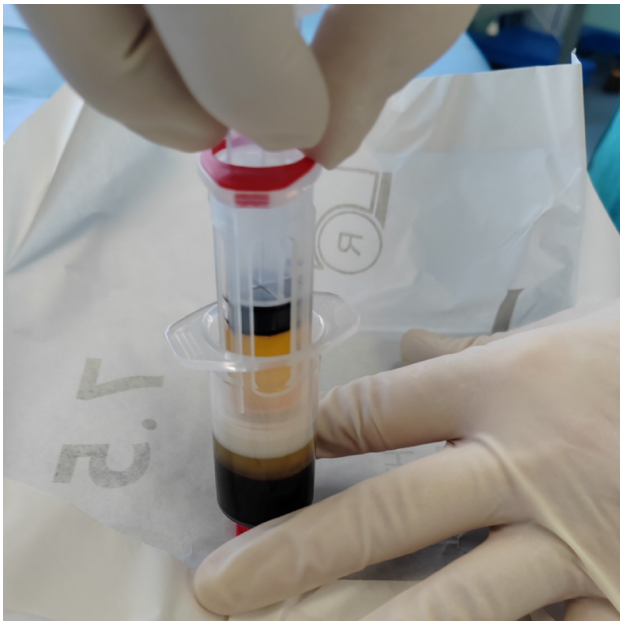

Figure 1 Platelet-rich plasma preparation technique. After centrifugation of 15 mL venous blood taken from the patient, approximately 5–6 mL of platelet-rich plasma was obtained with the Arthrex ACP® Double-Syringe System under sterile conditions.

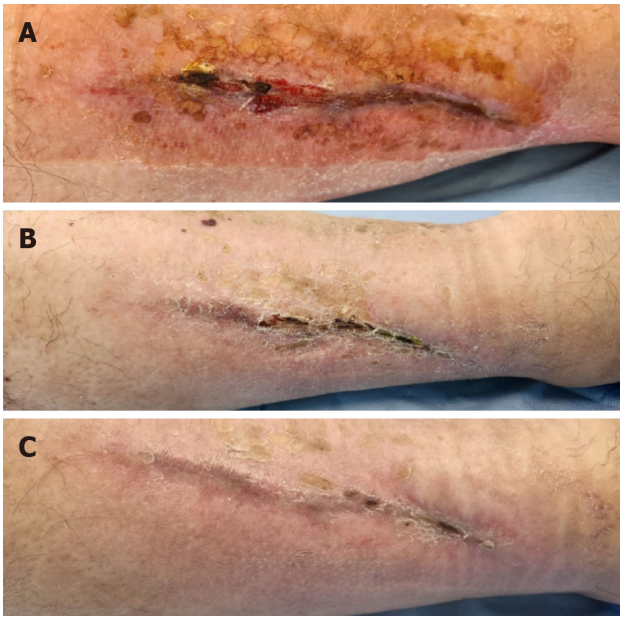

Figure 2 Wound images before and after the platelet-rich plasma treatment. A: Wound after the microbiological swab, showing physiological flora, and immediately before the platelet-rich plasma (PRP) treatment protocol. For size reference, a sterile cloth impression measuring 20 cm × 10 cm can be seen on the skin; B: Two weeks after the first application of autologous PRP, the wound had improved and was beginning to close from the proximal portion to distal. The wound was curved and extended from the middle of the lower leg to the proximal ankle; C: Two weeks after three PRP applications, a very good healing response was seen, with almost complete closure of the wound area.

Regenerative medicine in wound healing is a constantly developing area with novel strategies and PRP treatment as an important adjuvant biological therapy. Efficacy and safety are key factors for PRP usage, which is generally considered safe in autologous form. However, the lack of standardization and high-quality randomized controlled trials have been a matter of dispute[12,13]. PRP is used to treat a wide array of wound etiologies including diabetic, pressure ulcer, venous ulcer, surgical, or traumatic wounds, and wounds of other etiologies. As there are currently many case reports and series showing promising results, further evidence-based controlled clinical studies on the effectiveness of PRP are awaited with great interest[14-18].

There are different types of autologous PRP systems available on the market. Each preparation technique has different properties and specifications. Researchers are encouraged to state exactly which system was used in a study, so that further scientific analyses can be made. We used a preparation technique which removed white blood cells. A study comparing five different PRP preparation techniques in a single-donor model, including the Arthrex ACP®, showed

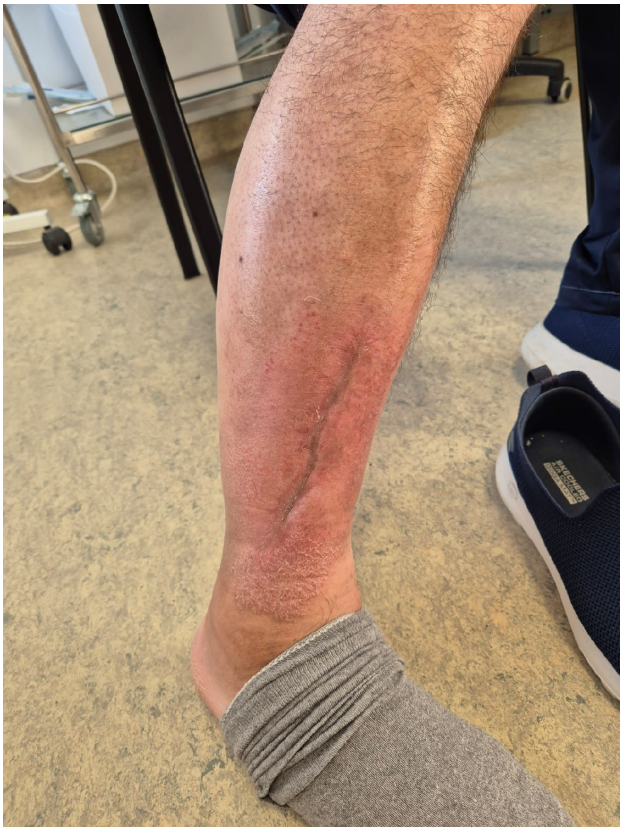

Figure 3 Healed wound at the follow-up appointment. Six months after the third autologous platelet-rich plasma injection, at the follow-up appointment, the patient was asymptomatic with preserved skin integrity in the former wound area. The chronic wound healed with complete restitution of the epithelial layer of the skin.

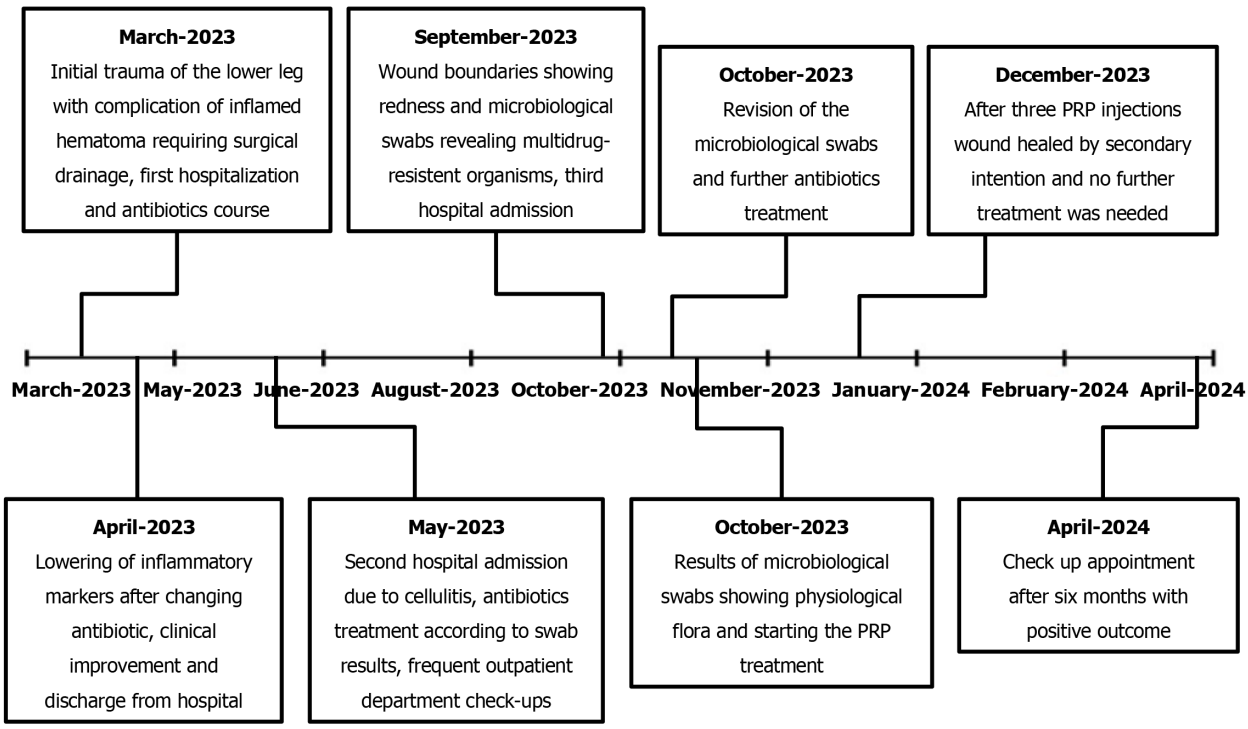

Figure 4 Case timeline. Overview of the wound management and course of treatment. PRP: Platelet-rich plasma.

positive correlations between platelet dose and VEGF dose, PDGF dose, EGF dose, and TGF-β1 dose of growth factors. Significant biological variations from different PRP preparation systems were studied, which may explain the noted differences and variability in clinical benefits reported in the literature. Most products are prepared in an autologous manner, with only a few minor adverse effects reported after treatment protocols with PRP. Variability of PRP preparation systems makes it difficult to properly analyze adverse effects, but inflammatory reactions could be due to the residual living cells in products containing leukocytes and freshly used products. These types of products may exacerbate local inflammatory responses; however, PRP treatment is considered safe and has a low rate of adverse effects[19,20]. Leukocytes containing products are sometimes referred to as L-PRP in the literature. Some key features of PRP preparations are that we can distinguish between high-platelet dose systems (usually 5—9 times higher concentrations of platelets than in blood) and low-platelet dose systems (2.5—3 times higher concentration) like the Arthrex ACP® system. The Mini GPS III Platelet Concentration System (Zimmer Biomet, Warsaw, IN, United States) is referred to as a system with high-platelet dose; however, the Arthrex ACP®, Regen PRP (RegenLab, Brooklyn, NY, United States), and Selphyl System (Selphyl, Bethlehem, PA, United States) are low-platelet dose systems. The Mini GPS III and Regen PRP systems produce PRP with high leukocyte concentrations, as opposed to the Selphyl System and the Arthrex ACP® system[19,21]. We are interested in new systems that we can offer to our patients, and new bio formulations, especially those that offer autologous regenerative treatment covered by medical insurance or at a reasonable surcharge for the patient.

Our experience with PRP treatment in our institution is mostly related to orthopedic cases, such as intra-articular injections for degenerative knee disease; we have had positive experiences, high patient compliance, and good clinical feedback from these treatments. This patient is the first case of PRP treatment of a chronic wound in our institution, and while we were in the process of publishing this paper, we commenced treatment of other patients suffering from chronic wounds of different origins, for example, diabetic foot ulcers. We are currently exploring new options for our institution. We have been using the Arthrex ACP® system, which was the only system available in our hospital at the time. Such treatment was covered by social medical insurance at a state level for pain treatment, including pain from chronic wounds. We are open to exploring other PRP systems, if they can offer better quality product and a high clinical rate of success in treating our patients. In this case, we only used photograph documentation and VAS score measurement, but other factors like wound depth, localization, vascularization, and different comorbidities could be considered for further analysis.

Studies analyzed in a meta-analysis from 2022 showed no serious side effects of PRP treatment in chronic wound management. Most studies report no side effects. There were some reports of pain in the injection area, contact dermatitis, and maceration[22]. A case series from 2017 analyzed patients with chronic non-healing ulcers treated with autologous PRP. The treatment demonstrated safety and efficacy with a mean time of ulcer healing of 8.2 weeks. Of note, PRP treatment was found to have the potential to prevent lower-extremity amputations caused by non-healing wounds and their complications, but this needs to be assessed further[18]. Tsai *et al*[23] compared PRP and platelet-derived patches treatment *vs* traditional advanced wound dressings in patients with chronic wounds in their randomized controlled trial from 2019. A statistically significant clinical improvement was observed in the PRP group after only 2 weeks, and an improved overall treatment success was observed in patients with diabetes. Platelet-derived patches may be considered as an adjuvant to classic autologous PRP injections in the future[23]. PRP can also be combined with ablative lasers or microneedling for various types of atrophic scars, with evidence of safety and efficacy[24].

As an alternative to PRP treatment, our patient could have undergone hyperbaric oxygen therapy (HBOT). This type of treatment is beneficial for the treatment of hypoxic wounds and is available through many different healthcare providers. Absolute and relative contraindications, particularly those regarding restrictive and obstructive airway diseases, should also be considered when recommending HBOT treatment to patients[25]. HBOT is used in diabetic foot ulcer treatment, and enhances short term healing; however, the long term effects and reduction of risk for major amputations are still debatable[26,27].

Studies have presented interesting results for the application of PRP for chronic ulcers; however, the absence of precise clinical protocols and guidelines limit the extension of its use. There is a need for robust clinical trials to determine the most accurate indication and preferred method of obtaining PRP and application protocols. The international scientific community should be encouraged to review the present study and related articles to advance this area of research[12,28]. The literature offers some implications that delivering higher doses of growth factors may be effective[29], but there is little evidence of greater effectiveness in chronic wound management with higher PRP dose. Final bio formulations and biological properties of PRP are still not conclusive, and the full potential of PRP treatment remains to be determined. Scientific efforts to reveal explicit roles of thrombocytes, leukocytes, growth factors, mesenchymal stem cells, and cell-to-cell interactions should be continued. The analgesic effects of PRP treatment should also be further assessed[30]. We are looking forward to well-documented clinical studies to establish the full potential of PRP treatment in wound healing and regenerative medicine.

CONCLUSION

Delayed wound healing and stable chronic wound patterns prone to complications are a clinical reality, usually with prolonged healing, high costs, and low-to-modest success rates. This case shows success of PRP application in achieving a complete skin integrity restitution in a long-standing, repeatedly infected chronic wound that did not respond to other conservative treatment modalities. Autologous PRP treatment may be a valuable, cost-effective alternative and possible adjuvant treatment for chronic wounds with poor healing tendency in selected patients. However, further research and standardization of protocols are urgently needed.

FOOTNOTES

Author contributions: Dimova A and Boroš M conceived of and designed the study; Dimova A, Dimov S, and Svetec M acquired the data; Dimova A, Boroš M, and Konjevod J drafted the manuscript; All authors analyzed and interpreted the data, critically reviewed the manuscript for important intellectual content, gave approval of the version to be submitted, and agree to be accountable for all aspects of the work.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict-of-interest statement: The authors declare no competing interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country of origin: Croatia

ORCID number: Ana Dimova 0009-0007-4603-9567; Martin Boroš 0000-0002-0488-4398; Janja Konjevod 0009-0004-7426-7311.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zheng XM

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6644-6646

DOI: 10.12998/wjcc.v12.i33.6644

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Tricuspid mass-curious case of Li-Fraumeni syndrome: A letter to the editor

Mohammad S Al-Haggar, Zahraa A Abdelmoneim

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade A

Creativity or Innovation: Grade B

Scientific Significance: Grade A

P-Reviewer: Wang XD

Received: March 6, 2024

Revised: August 3, 2024

Accepted: September 19, 2024

Published online: November 26, 2024

Processing time: 204 Days and 19.3 Hours

Mohammad S Al-Haggar, Department of Pediatrics and Genetics, Mansoura University Children's Hospital, Mansoura 35516, Egypt

Zahraa A Abdelmoneim, Department of Pediatrics, Genetic Unit, Mansoura University Children Hospital, Mansoura 35516, Egypt

Corresponding author: Zahraa A Abdelmoneim, MD, Lecturer, Department of Pediatrics, Genetic Unit, Mansoura University Children Hospital, EL Gomhoria Street, Mansoura 35516, Egypt. hzahraa211@gmail.com

Abstract

We focus specifically on the rare occurrence of cardiac thrombi in Li-Fraumeni syndrome (LFS). LFS is a hereditary risk to a diverse range of specific, uncommon, malignancies. Children and young adults have a heightened susceptibility to many malignancies, particularly soft-tissue and bone tumors, breast malignancies, central nervous system malignancies, adrenocortical carcinoma, and blood cancers. Additionally, LFS patients may experience other cancer types such as gastrointestinal, lung, kidney, thyroid, and skin cancers, along with those affecting gonadal organs (ovaries, testicles, and prostate). An accurate diagnosis of LFS is crucial to enable affected families to access appropriate genetic counseling and undergo surveillance for early cancer detection.

Key Words: Li-Fraumeni syndrome; Cancers; Cardiac thrombus; Genetic counseling; Surveillance

Core Tip: Li-Fraumeni syndrome (LFS) is an inherited propensity to various distinct, frequently uncommon malignancies. Pediatric and adolescent age groups are more likely to acquire many malignancies, including soft-tissue and bone tumors, breast cancer, central nervous system cancers, adrenocortical carcinoma, and blood cancers. LFS individuals may also develop various types of cancer, including gastrointestinal, lung, kidney, thyroid, and skin cancers, as well as those affecting the gonadal organs. An accurate diagnosis of LFS is critical for afflicted families to receive appropriate genetic counseling and be monitored for early cancer detection.

Citation: Al-Haggar MS, Abdelmoneim ZA. Tricuspid mass-curious case of Li-Fraumeni syndrome: A letter to the editor. *World J Clin Cases* 2024; 12(33): 6644-6646
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6644.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6644

TO THE EDITOR

Li-Fraumeni syndrome (LFS) is linked to elevated susceptibility to a wide range of cancers occurring in all age groups[1]. Individuals with LFS face a lifelong cancer risk of at least 70% for men and over 90% for women. The most common malignancies in LFS include adrenocortical malignancies, breast malignancies, nervous system malignancies, bone malignancies, and soft-tissue malignancies. LFS is connected with an elevated occurrence of multiple cancer forms, including leukemia, lymphomas, gastrointestinal cancers, prenatal choriocarcinoma, and other reported malignancies[2,3].

LFS diagnosis is confirmed when a proband fulfills all three traditional LFS criteria and/or presents a pathogenic (or likely pathogenic) germline variant in *TP53* detected through molecular analysis. Typical LFS criteria (60%-80% show a germline *TP53* harmful mutation)[2]: (1) A patient has a sarcoma diagnosed before the age of 45; (2) A first-degree relative has malignancy before the age of 45; and (3) A first- or second-degree relative has malignancy before 45, or with sarcoma at any age.

The Chompret criteria for clinical diagnosis of LFS has new diagnostic tools to detect diseased individuals in addition to the conventional items described before. Anyone with a personal and family history that fits one of the following three criteria may be diagnosed with LFS and tested for the *TP53* gene mutation:

Criterion 1: A tumor from the LFS cancer spectrum diagnosed before the age of 46. This includes soft tissue sarcoma, bone tumor, pre-menopausal breast malignancy, central nervous system (CNS) cancer, adrenal cortical malignancy, blood cancer, and lung malignancy.

At least one first- or second-degree family member has an LFS-related cancer, with the exception of breast cancer if the individual is under the age of 56 or has several cancers.

Criterion 2: An individual with various cancers, excluding many breast malignancies, two of them are on the LFS cancer spectrum, and the first of them developed before the age of 46 (A case report).

Criterion 3: An individual has adrenocortical carcinoma or a malignancy in the choroid plexus, which is a membrane surrounding the brain, independent of family history.

Furthermore, individuals have anaplastic rhabdomyosarcoma, females with breast malignancy before the age of 31, and individuals have hypodiploid acute lymphoblastic leukemia and SHH medulloblastoma, regardless of family history, should be evaluated.

The documented case[1] involved a 30-year-old female patient with a background of multiple cancers meeting the criteria for LFS. She visited the cardio-oncology clinic after a heart tumor in the right ventricle was discovered with follow up echocardiogram, which was being performed to monitor two atrial septal defects. During her assessment, she reported no recent symptoms such as chest discomfort, palpitations, exertional dyspnea, orthopnea, or peripheral edema. Clinical examination revealed no signs of murmurs, arrhythmias, jugular venous distention, lung crepitation, or leg swelling. A transthoracic echocardiogram identified a 1 cm × 1 cm mass near the tricuspid valve. The patient subsequently had a cardiothoracic operation, during which a biopsy revealed a 2 cm mass on the posterior leaflet of the tricuspid valve with a slender stalk. The mass was excised from the stalk, and the specimen was found to be a large, structured thrombus without malignancy. Additionally, her atrial septal defects were repaired during the surgery. Her surgical repair was uncomplicated.

The case report[1] did not mention the exclusion or discussion of other potential causes of a cardiac thrombus, such as the type of chemotherapy that the patient received, history of central venous catheter insertion, or any additional symptoms or signs suggestive of infective endocarditis.

CLINICAL IMPLICATIONS

Diagnosing LFS necessitates regular oncological management and surveillance for malignancies to prevent their occurrence. Surveillance involves a thorough clinical assessment and imaging of the abdomen and pelvis every 3-4 months from birth until age 18. Additionally, a yearly CNS examination and whole-body magnetic resonance imaging (MRI), including a brain MRI, are required at onset of diagnosis.

For patients 18 years and older, a clinical examination should be conducted every six months, with an annual imaging of the abdomen and pelvis and a skin examination. Females should undergo a physical breast assessment every 6-12 months starting at age 20-25, an annual breast MRI starting at age 20-30, and a mammogram along with a breast MRI annually from age 30 to 75. Upper endoscopy and colonoscopy are needed every 2–5 years starting at age 25[4,5].

Genetic counseling is crucial, as LFS is inherited in an autosomal dominant pattern. Patients with LFS have inherited a *TP53* harmful mutation from one parent, while 7-20% have a *de novo TP53* pathogenic variant. Children of someone with an established LFS diagnosis (meeting typical LFS criteria or having a heterozygous germline *TP53* harmful mutation) have a 50% chance of having the variant and the associated cancer risks. Predictive testing for at-risk family members, as

well as prenatal and preimplantation molecular analysis, are available if a *TP53* germline harmful mutation is identified in the family[6].

LFS is an uncommon genetic condition that elevates the occurrence of various malignancies. Detecting this syndrome requires monitoring for additional malignancies and providing thorough genetic counseling to enable early diagnosis and treatment of cancers. The presence of intracardiac thrombus in such cases requires further confirmation by ruling out other causes of cardiac thrombi and through molecular testing.

FOOTNOTES

Author contributions: Al-Haggar MS revised the manuscript; Abdelmoneim ZA wrote the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country of origin: Egypt

ORCID number: Zahraa A Abdelmoneim 0009-0005-3632-6410.

S-Editor: Li L
L-Editor: A
P-Editor: Zheng XM

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6647-6649

DOI: 10.12998/wjcc.v12.i33.6647

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Secondary diabetes due to different etiologies: A problem worthy of attention

Zhao Wei, Xue-Jian Wang

Specialty type: Neurosciences

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Zhang J

Received: April 21, 2024
Revised: September 6, 2024
Accepted: September 23, 2024
Published online: November 26, 2024
Processing time: 158 Days and 18.1 Hours

Zhao Wei, Xue-Jian Wang, Department of Neurosurgery, Affiliated Hospital 2 of Nantong University, Nantong 226000, Jiangsu Province, China

Co-first authors: Zhao Wei and Xue-Jian Wang.

Corresponding author: Xue-Jian Wang, MD, PhD, Doctor, Department of Neurosurgery, Affiliated Hospital 2 of Nantong University, No. 666 Shengli Road, Chongchuan District, Nantong 226000, Jiangsu Province, China. 6841441@163.com

Abstract

There are many factors in the occurrence of diabetes, which can result in insufficient insulin secretion and insulin receptor resistance. Including pituitary tumors, can also lead to the occurrence of diabetes, if the primary disease can not be well controlled in time, such secondary diabetes control is more difficult. In the process of clinical diagnosis and treatment, these factors need to be taken into account, timely detection and treatment of primary diseases, so as to reduce the possibility of clinical missed diagnosis.

Key Words: Editorial; Secondary diabetes; Different etiologies; Pituitary tumors

Core Tip: There are many factors in the occurrence of diabetes, which can result in insufficient insulin secretion and insulin receptor resistance. Including pituitary tumors, can also lead to the occurrence of diabetes, if the primary disease can not be well controlled in time, such secondary diabetes control is more difficult.

Citation: Wei Z, Wang XJ. Secondary diabetes due to different etiologies: A problem worthy of attention. *World J Clin Cases* 2024; 12(33): 6647-6649
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6647.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6647

TO THE EDITOR

In this editorial, we present our comments on the article by Song *et al*[1]. Secondary diabetes is a type of diabetes that has a specific cause and is often misdiagnosed clinically as the common type 2 diabetes, especially when it is caused by some rare diseases[2]. It does not stem from problems with islet function itself, as in primary diabetes. Common causes include endocrine diseases, the use of certain drugs, genetic factors, *etc*., such as Williams-Beuren syndrome[3], Prader-Willi syndrome[4], pituitary adenoma, and IGG4-related diseases[5]. Four patients are listed in the form of case reports. We have also treated patients with growth hormone adenomas with diabetes, and in the course of treatment, we found a correlation between the two.

SECONDARY DIABETES ASSOCIATED WITH PITUITARY TUMORS

Pituitary tumors may lead to secondary diabetes, such as growth hormone adenomas and adrenocorticotrophin adenomas are particularly responsible for this disease[6,7]. Most of the patients with growth hormone adenoma often have serious complications such as abnormal glucose metabolism, hypertension, myocardial hypertrophy and respiratory diseases when they are treated. In addition, other axial systems of the anterior pituitary gland, such as the destruction of the gonadal axis function, seriously affect the quality and life span of patients[8]. The main metabolic function of GH is lipolysis, increasing the free fatty acids in the blood, which compete with glucose for binding sites on the muscle, inhibit glucose uptake, and produce insulin resistance, insulin signal transduction disorder is one of the main reasons for insulin resistance in type 2 diabetes patients. In addition, GH stimulates gluconeogenesis and inhibits muscle glycogen synthase. Insulin resistance is a recognized risk factor for cardiovascular diseases. Hyperinsulinemia can increase the incidence of cardiovascular diseases and mortality in patients with acromegaly. Controlling the disease and improving glucose homeostasis can reduce the incidence of cardiovascular diseases. Compared with the general population, diabetes is more likely to occur in patients with acromegaly[9], and diabetes will increase the mortality of patients with acromegaly[10].

The above examples suggest that there are many sources of secondary diabetes and that it is highly harmful. For such diseases, a comprehensive consideration should be taken in the diagnosis, including the presence of other disease bases and manifestations, as well as blood sugar levels and other relevant indicators[11].

In addition, for the treatment of some diseases, especially somatogen pituitary tumors, it is required to complete the preoperative examination of pituitary tumors, and also to clarify the possibility of other complications such as blood sugar control[12]. Clinical advice is to strengthen the control of blood sugar and basically achieve normal surgery to prevent adverse consequences. However, due to abnormally high hormones, some patients may have obvious blood sugar fluctuations, and blood sugar is not easy to control, which requires the coordination and participation of endocrinologists, neurosurgeons and other departments[13].

CONCLUSION

To sum up, clinicians should pay attention to improve the examination for the diagnosis and treatment of diseases to prevent missed diagnosis and misdiagnosis. Only by giving patients a comprehensive diagnosis and treatment can we achieve better therapeutic effect.

FOOTNOTES

Author contributions: Wang XJ designed the overall concept, discussion and outline of the manuscript; W Zhao contributed to the discussion and design of the manuscript; Wang XJ contributed to the writing and editing of the manuscript and review of the literature.

Supported by Traditional Chinese medicine science and technology project in Jiangsu province, No. YB2015113; the Science and Technology Program of Nantong Health Committee, No. MA2019003, and No. MA2019003; Science and Technology Program of Nantong City, No. Key003, and No. JCZ2022040; Kangda College of Nanjing Medical University, No. KD2022KYJJZD019, No. KD2021JYYJYB025, and No. KD2022KYJJZD022.

Conflict-of-interest statement: All authors have no any conflicts of interest.

Country of origin: China

ORCID number: Xue-Jian Wang 0000-0003-0389-5674.

Corresponding Author's Membership in Professional Societies: American Association for Peripheral Neurosurgery, No. 5300190.

S-Editor: Liu JH
L-Editor: A
P-Editor: Cai YX

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6650-6654

DOI: 10.12998/wjcc.v12.i33.6650

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Flexner's legacy and the future of medical education: Embracing challenge and opportunity

Quzhen Zeren, Yan Zeng, Jun-Wen Zhang, Jian Yang

Specialty type: Health policy and services

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade B

P-Reviewer: Varama A; Zhang Z

Received: April 29, 2024

Revised: September 16, 2024

Accepted: September 23, 2024

Published online: November 26, 2024

Processing time: 150 Days and 11.5 Hours

Quzhen Zeren, Department of Gastroenterology, Changdu People's Hospital of Xizang, Changdu 854000, Tibet Autonomous Region, China

Yan Zeng, Department of Psychology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

Jun-Wen Zhang, Jian Yang, Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Corresponding author: Jian Yang, MD, PhD, Associate Chief Physician, Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, China. yangjian@hospital.cqmu.edu.cn

Abstract

This editorial comments on the article by Alzerwi. We focus on the development course, present challenges, and future perspectives of medical education. Modern medical education is gradually undergoing significant and profound changes worldwide. The emergence of new ideas, methodologies, and techniques has created opportunities for medical education developments and brought new concerns and challenges, ultimately promoting virtuous progress in medical education reform. The sustainable development of medical education needs joint efforts and support from governments, medical colleges, hospitals, researchers, administrators, and educators.

Key Words: Medical education; Medical education reform; Abraham Flexner's report; Educational administration; Challenge and opportunity

Core Tip: Medical education is never invariable, but it keeps pace with the times and is constantly influenced by multiple factors. Reviewing the past and analyzing the present of modern education and medical practice will help move forward better and faster in the new era. The emergence of new ideas, methodologies, and technologies has created opportunities for the development of medical education and also brought new concerns and challenges worthy of contemplation and continuous exploration by every researcher, administrator, and educator concerned about the reform and development of medical education.

Citation: Zeren Q, Zeng Y, Zhang JW, Yang J. Flexner's legacy and the future of medical education: Embracing challenge and opportunity. *World J Clin Cases* 2024; 12(33): 6650-6654
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6650.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6650

TO THE EDITOR

Medical education is significant in promoting the sustainable and healthy development of health care, the primary way to cultivate qualified medical workers, and makes decisive contributions to the level and quality of medical and health services in a country or region. In addition, medical education also promotes the innovation and development of medical and health care to adapt to the progress of society and the economy. Meanwhile, modern medical education is global, with worldwide efforts to implement competency-based reform and innovations to address the issues arising during the education process and to meet local and international healthcare needs[1].

We are very interested in the original article by Alzerwi[2]. We consider this a qualified and enlightening study, as the authors reviewed multiple reforms for medical education in Abraham Flexner's seminal 1910 report and the evolution of the medical education system since the 19th century, enumerated current problems in medical education (terming them as returning to the pre-Flexnerian state), emphasized the importance of basic science, and suggested a return to Flexner's recommendations. This article would undoubtedly stimulate more interest and attention in medical education among researchers and educators, help solve current problems, and further adapt to the new situation and needs of global health care and medical education.

PROPOSAL AND DEVELOPMENT OF THE FLEXNER REPORT

In the late 19th century, education in most American medical colleges was still solely focused on imparting students the practical application of existing medical knowledge. A series of pioneers and institutions, including The Johns Hopkins University and its School of Medicine, proposed the particularity of medical education and gave rise to scientifically based medical education[3].

More than a century ago, Abraham Flexner visited and investigated 155 medical schools and then released the famous "Herculean Report on Medical Education in the United States and Canada" to the public in June 1910[4]. Flexner's report made numerous recommendations for medical education, including a solid scientific basis and the applications of pedagogical methods, and therefore had a profound impact on the reform and practice of medical education[5]. Despite some controversy[6,7], the report ushered in a new era in modern medical education.

For over a century, Flexner's report has undoubtedly facilitated the reform and development of global medical education and laid a solid foundation for training higher-quality medical talents. In recent years, there have been varying declines in the number of clinical researchers, bedside teaching, and faculty-supervised patient interactions, and contrary increases in student absenteeism and working hours in front of a computer, as Alzerwi[2] mentioned.

While raising these worries above, we also recognize that medical practice in the current era is dramatically affected by many factors, such as data science, new medical technology, medical policy, and demographic changes, and therefore, medical education also needs to be adjusted accordingly[8]. Meanwhile, multiple challenges and opportunities have arisen for medical education after the coronavirus disease 2019 (COVID-19) pandemic, including the exploding application of information technology, the rapid development of interprofessional education, and increasing concerns about health disparities worldwide[9]. Review the past to understand the present. While there is no guarantee that the current medical education reform and evolution will solve all of today's problems, it is believed that we are in the right direction in the present and future, led by many pioneers, including Abraham Flexner.

CHALLENGES TO CURRENT MEDICAL EDUCATION

Challenges to current medical education are multifaceted, and their reasons vary. In addition to the shortage of clinical researchers, the decrease in bedside teaching, the increase in student absenteeism, and the weakening of the teachers' role, which Alzerwi[2] has already mentioned, current challenges also include the weak inclusion of medical humanities, the continuous emergence and multiple impacts of new educational methodologies, and the reshaping of medical education

and practice models by new technologies.

The first aspect to consider is insufficient medical humanities in current medical education. Although many would disagree and may point out that numerous medical schools worldwide have already added medical humanities to undergraduate curricula, there is no denying the subordinate role of medical humanities in current medical education [10]. The current medical humanities education mainly acquires knowledge from humanities passively and lacks insight from medicine to humanities[11]. Not only that, even among medical humanities supporters, there is still a lack of consensus on the teaching content and pedagogy[12]. Meanwhile, although the importance of medical humanities in shaping students' empathy and positive values has been well acknowledged, medical interns may be confused by a series of disconnections between pre-clinical education and clinical practice, especially when witnessing compassion always outsourced to nurses. Therefore, the purpose of teaching medical humanities should not only be to introduce a specific known knowledge but to integrate medical humanities as a priority pattern of clinical thoughts and behaviors into medical students' future careers[13,14].

The second aspect is the emergence of various new pedagogical approaches and theories and their multiple impact. New teaching methodologies are mainly to adapt to the needs of medical and social developments. Although traditional teaching methods can help students learn medical concepts and theories comprehensively and systematically, they can neither satisfactorily consider the cultivation of practical ability and innovative thinking nor keep pace with the variation in global emerging diseases and education needs. In this context, a series of novel teaching methods, including problem-based learning, case-based learning, and task-based learning, gradually came into being and have revealed a positive influence on medical education[15]. However, recent studies have also shown that these new teaching methodologies are only used in a subset of medical schools and, in most cases, only for a small proportion of students[16]. The reasons for this are manifold, not only because the new teaching methods may not be suitable for every district, medical school, and student but also because of insufficient funding, relatively cumbersome processes, extra burdens for educators, and their resistance to the new methodologies[17]. In online teaching and clinical simulation teaching[18,19], which have gradually emerged since the COVID-19 era, there are also situations similar to the above where progress caused by new methodologies coexists with various influences that cannot be ignored. Therefore, we need not only to promote the latest methods to adapt to the needs of the new era and obtain better teaching results but also to carry out further research and continuously update these above methodologies.

The third aspect is new technologies reshaping medical education and practice models. First of all, the increasing applications of modern teaching platforms such as podcasts, social media, and video conferencing brought about by the development of digital technologies have made learning more attractive and interactive while also helping to overcome geographical constraints[20], which has been further developed since the times of COVID-19[21]. However, some researchers have claimed that digitizing medical education would reduce the difficulty of obtaining medical information and make medical professionals lazy and forgetful[22]. The next is the rapid development of artificial intelligence (AI) technology in recent years. AI can be applied in medical teaching implementation, teaching evaluation, and teaching feedback. Since AI technology has already and will continue to have a profound impact on medical practice in the future, medical education should pay more attention to the combination of man and machine in medical teaching and training and accordingly integrate AI technology into current education so that future medical professionals can better improve learning ability and clinical performance[23]. Although recent surveys have shown that most students hold positive perceptions of AI[24], the appropriate level of AI education for varied medical students may be a difficult decision for medical schools and educators[25]. Technological progress is a double-edged sword, and fear is understandable. However, resistance can not stop the pace of continuous technical development; only the brave embrace of new technology can help us remain irreplaceable in the unknown future.

In addition to these above challenges, there are still more unsolved problems, such as imperfect education systems, uneven education resources, lack of teaching team construction, unsatisfactory quality of student training, deficient training capacity for major infectious diseases, insufficient integration of multi-disciplines, and declining senses of professional honor. Although there seem to be plenty of problems, finding problems is the premise of analyzing and solving them, and it is also the only way to improve and progress medical education. Overall, we should have complete confidence in the future.

OPPORTUNITIES AND FUTURE PATH

Reference Citation Analysis (*RCA*, https://www.referencecitationanalysis.com/) is a unique artificial intelligence system for citation evaluation of biomedical literature. *RCA* was employed to analyze previous studies on medical education reform up to December 2023. Database retrieval has revealed that the published literature on medical education reform in the past five years has far exceeded those in the first decade of the 21st century. With the rapid development of high and new technology, the research of medical education reform has also ushered in a new peak. Where is the future of medical education headed?

It is foreseeable that medical education will usher in another remarkable development, especially with the application of artificial intelligence, virtual reality, telemedicine, and other technologies[26], providing more opportunities and possibilities for medical education. At the same time, international cooperation in medical education will be further strengthened along with the trend of globalization[27]. The world's advanced medical education concepts and methodologies will be promoted and applied more quickly than ever, contributing to the reasonable distribution of global medical education resources. Countries and regions worldwide will also continue to increase policy support and financial investment in medical education and create a suitable environment for the further development of medical education[28].

However, the path to the foreseeable future is uncertain and not unique. A timely review of the incompatibility between Flexner's recommendations and the current education practice is necessary and an important guarantee to continue the rapid development of medical education for more than a century. Meanwhile, we should recognize that reviewing the past is not for the sake of being confined to the past but for the sake of new development. It is also necessary to effectively combine the current world economic and social development and the updated medical practice needs, boldly innovate in the land of medical education practice, "plant new trees" with new methodologies and bear fresh fruits of development in the new era. In addition, the problem of student absenteeism mentioned in Alzerwi[2]'s article may not become a problem as medical schools may reduce their non-unique pre-clinical classroom training in the future[29]. In the meantime, although the specific development process may vary markedly in different regions[30], insufficient bedside teaching mentioned by Alzerwi[2] may also be alleviated with the popularization of artificial intelligence and virtual simulation teaching technology[31].

CONCLUSION

In the current coexistence of problems and opportunities, medical education in the new era has ushered in a unique and profound development opportunity. Under the updated medical needs requirements, with the help of high-tech and new teaching methodologies, medical education reform will go faster and better based on our predecessors.

FOOTNOTES

Author contributions: Zeng Y, Yang J, and Zhang JW conceptualized and designed the research; Zeren Q and Yang J performed the literature search, analyzed the data, and wrote the original manuscript; Zeng Y and Zhang JW edited the final manuscript; All authors have read and approved the final manuscript.

Supported by Education and Teaching Reform Project of the First Clinical College of Chongqing Medical University, No. CMER202305; Program for Youth Innovation in Future Medicine, Chongqing Medical University, No. W0138; and Natural Science Foundation of Tibet Autonomous Region, No. XZ2024ZR-ZY100(Z).

Conflict-of-interest statement: All authors have declared that they have no conflict-of-interest to disclose.

Country of origin: China

ORCID number: Yan Zeng 0000-0003-4935-1306; Jun-Wen Zhang 0000-0003-2911-598X; Jian Yang 0000-0001-8170-0727.

Corresponding Author's Membership in Professional Societies: Chinese Medical Association, M0100446703M.

S-Editor: Liu JH
L-Editor: A
P-Editor: Cai YX

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6655-6659

DOI: 10.12998/wjcc.v12.i33.6655

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Targeting nuclear factor erythroid 2-related factor 2-regulated ferroptosis to treat nervous system diseases

Ye-Qi Huang, Zheng-Wei Huang, Xue-Juan Zhang

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade B
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Mo ZM

Received: May 22, 2024
Revised: September 11, 2024
Accepted: September 19, 2024
Published online: November 26, 2024
Processing time: 127 Days and 12.5 Hours

Ye-Qi Huang, Zheng-Wei Huang, Xue-Juan Zhang, College of Pharmacy, Jinan University, Guangzhou 510006, Guangdong Province, China

Co-corresponding authors: Zheng-Wei Huang and Xue-Juan Zhang.

Corresponding author: Zheng-Wei Huang, PharmD, Teacher, College of Pharmacy, Jinan University, No. 855 East Xingye Dadao, Panyu District, Guangzhou 510006, Guangdong Province, China. huangzhengw@jnu.edu.cn

Abstract

By critically examining the work, we conducted a comprehensive bibliometric analysis on the role of nuclear factor erythroid 2-related factor 2 (NRF2) in nervous system diseases. We also proposed suggestions for future bibliometric studies, including the integration of multiple websites, analytical tools, and analytical approaches, The findings presented provide compelling evidence that ferroptosis is closely associated with the therapeutic challenges of nervous system diseases. Targeted modulation of NRF2 to regulate ferroptosis holds substantial potential for effectively treating these diseases. Future NRF2-related research should not only focus on discovering new drugs but also on designing rational drug delivery systems. In particular, nanocarriers offer substantial potential for facilitating the clinical translation of NRF2 research and addressing existing issues related to NRF2-related drugs.

Key Words: Bibliometric; Nervous system diseases; Nuclear factor erythroid 2-related factor 2; Ferroptosis; Target

Core Tip: Based on the original paper, this study highlights two primary points: Bibliometric methodologies and future perspectives for nuclear factor erythroid 2-related factor 2 (NRF2) research. We emphasize the need for broader literature databases and diversified analysis methods in bibliometric research. Additionally, we highlight the importance of NRF2 modulation in regulating ferroptosis for treating nervous system diseases and discuss how nanoparticle drug delivery systems may overcome challenges associated with NRF2-related drugs.

Citation: Huang YQ, Huang ZW, Zhang XJ. Targeting nuclear factor erythroid 2-related factor 2-regulated ferroptosis to treat nervous system diseases. *World J Clin Cases* 2024; 12(33): 6655-6659
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6655.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6655

TO THE EDITOR

We have thoroughly examined the high-quality bibliometric study by Chang *et al*[1], published in the high-impact journal, *World Journal of Clinical Cases*. In this study, a bibliometric analysis of the literature was conducted to provide a comprehensive overview of trends in evolutionary research trends on nuclear factor erythroid 2-related factor 2 (NRF2) in the nervous system disease, including focal points, frontiers, and potential future directions. The main content of the study is summarized in Table 1.

Herein, we critically analyze the paper by Chang *et al*[1] focusing on two aspects, *i.e.*, bibliometric methodologies and future perspectives, to stimulate constructive discussion in clinical and basic research communities. It will be our great pleasure to receive a response from the author team soon.

BIBLIOMETRIC METHODOLOGIES

The conceptualization and design of the bibliometric study were acceptable. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline-followed recruitment approach was illustrated. The analyzed results were relatively convincing and the discussion was appealing. The obtained findings can serve as a reference for future research on neurological diseases.

Chang *et al*[1] commented on the limitations of their study. Based on this, we suggest the following for future bibliometric studies.

Incorporating data from a broader spectrum of literature

First, it is suggested to expand the range of literature databases used. Although the Web of Science Core Collection is highly trusted, other major databases such as Scopus, PubMed, and Google Scholar are recommended for cross-comparison. Second, the diversity of the TS can be improved including core clinical topics from the published literature on nervous system disorders. Using these approaches will provide access to a wider range of sources and diverse literature, enhancing the comprehensiveness and credibility of bibliometric analyses.

Acquiring more bibliometric information

Additional bibliometric tools and various bibliometric analytical methods can be used. Besides CiteSpace, other important software or online platforms like VOSviewer, SATI, HistCite, can be utilized for indicator analysis and visual representation. Additionally, statistical analysis and co-word analysis can be conducted alongside citation and cluster analyses to gain deeper insights.

Enhancing the dimensions of the discussion on the results

The integration of strengths, weaknesses, opportunities, and threats (SWOT) analysis is an effective approach. SWOT analysis includes problem diagnosis and prescription. Through a comprehensive analysis of internal and external factors, SWOT analysis assists in identifying the research object's current capabilities and potential for further development[2]. This analysis has been comprehensively applied in medical and biomedical sciences[3,4]. The inclusion of SWOT analysis can offer more valuable information and implications to the status quo and future directions in these fields of research.

By incorporating a broader spectrum of literature, acquiring more bibliometric information, and enhancing the dimensions of the discussion on the results, bibliometric investigations will become more informative.

FUTURE PERSPECTIVES

Importantly, as revealed by the study focus and frontiers in the original paper, the regulation of ferroptosis by NRF2 in nervous system cells has been a research hotspot in this field. NRF2 was first reported to participate in ferroptosis regulation by Sun *et al*[5] in 2016. In the study, the p62-Keap1-NRF2 antioxidative signaling pathway was identified as a crucial negative regulator of ferroptosis in hepatocellular carcinoma cells, exerting its effect through the transcriptional activation of genes involved in reactive oxygen species and iron metabolism. Up to now, ferroptosis has been shown to play an important role not only in the treatment of nervous system diseases but also in various cancer types. The regulatory pathways associated with NRF2 in diverse diseases have been widely examined and can be summarized as follows.

Table 1 Main content of the original paper

Item	Details
Background	NRF2, a pivotal transcription factor in the antioxidant network, has been reported to play a crucial role in nervous system diseases. susceptible to oxidative damage. Consequently, the regulatory capacity of NRF2 and its potential clinical applications in these diseases have generated increasing interest in the scientific community
Methods	Data were gathered through a systematic review of the literature on NRF2 and nervous system diseases from the Web of Science Core Collection database and used the bibliometric tool CiteSpace for analysis
Results	Recent years have seen a rise in NRF2-related literature on nervous system diseases, with China holding a dominant position in terms of article publications, financial investments, and the number of authors with the highest publication records. NRF2 research hotspots have evolved from focusing solely on antioxidants to include anti-apoptosis and active ferroptosis
Conclusion	China should prioritize enhancing the quality and impact of research articles. Research on NRF2 in nervous system diseases has expanded to encompass various cell death mechanisms. Further clinical investigations of NRF2-related medications are necessary

NRF2: Nuclear factor erythroid 2-related factor 2.

Antioxidative activities

The NRF2 signaling pathway is intricately associated with multiple pathways involved in oxidoreductase synthesis, which plays an overlooked role in the process of ferroptosis. Specifically, the downstream targets of NRF2 encompass nicotinamide adenine dinucleotide phosphate [NAD(P)H] quinone oxidoreductase 1, heme oxygenase-1 (HO-1), solute carrier family 7 membrane 11, NAD(P)H quinone oxidoreductase 1, thioredoxin 1, phase II detoxifying enzymes, and various multidrug resistance-associated transporters[6,7].

Iron homeostasis

Notably, NRF2 plays a crucial role in maintaining iron homeostasis, thereby influencing cell susceptibility to ferroptosis through its impact on free radical generation and lipid peroxidation[8]. For instance, NRF2 has been reported to control HERC2 (E3 ubiquitin ligase for nuclear receptor coactivator 4 and F-box/LRR-repeat protein 5), and vesicle-associated membrane proteins 8 (which mediates autophagosome-lysosome fusion) for the maintenance of iron homeostasis[9]. Additionally, various iron-related proteins such as ferritin, transferrin receptor, ferroportin, and HO-1 have been shown to be with NRF2[10,11]. In a nutshell, NRF2 is an inhibitor of ferroptosis.

The elucidation of the above-mentioned regulatory mechanisms contributes to a deeper understanding of NRF2's role in nervous system diseases. It is well documented that multiple nervous system diseases, such as central nervous system injury (ischemic stroke, hemorrhage, and spinal cord injury)[12], neurodegenerative disease, such as Huntington's disease, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis[13], and the brain cancers[14] are closely related to upregulated ferroptosis processes. For instance, the induction of ferroptosis has been shown to effectively suppress glioblastoma cells through the downregulation of the protein kinase B/mammalian target of rapamycin complex 1/glutathione peroxidase 4 signaling pathway in the study by Cai *et al*[15] in 2023. Suppressing the ferroptosis level in damaged cells is a reasonable and promising strategy to manage the above-mentioned nervous system diseases.

From this point of view, to upregulate NRF2 expression, by downregulating the expression of NRF2 competition factors like bric-a-brac and cap-n-collar homology 1[16], or activate the NRF2-involved signaling pathways, *e.g.* vitamin D receptor/NRF2/HO-1 pathway[17], Keap1-NRF2-ARE pathway[18], will become a ferroptosis-targeted therapy for nervous system diseases. Numerous NRF2 activators have entered clinical trials, highlighting their potential therapeutic applications[19]. Dimethyl fumarate (DMF), which has demonstrated the ability to induce NRF2 activation within the central nervous system, has been approved for psoriasis treatment[20]. Additionally, another NRF2 agonist, cyanoenone triterpenoid RTA-408 (omaveloxolone), was reported in a phase 2 randomized clinical trial to be well tolerated and to enhance neurological function when administered at a dosage of 160 mg/day over 12 weeks[21]. These findings underscore the significant clinical value of targeted NRF2 therapy and its growing prominence in research. To achieve the above targeted therapy, the utilization of various drugs, consistent with the findings of Chang *et al*[1], particularly, bioactive compounds from traditional Chinese medicine has been documented in relevant research. For instance, Salidroside[22], Forsythoside A[23], DMFs[24], Trehalose[25], Berberine[26], *etc.*, and exerted promising activities.

Furthermore, sophisticated nanocarriers can be designed to deliver the corresponding therapeutics to enhance the efficacy of ferroptosis-targeted therapy for nervous system diseases. Nanocarriers, *e.g.*, lipid nanoparticles (*e.g.* liposomes), polymeric nanoparticles (*e.g.* polymeric micelles), and protein nanoparticles (*e.g.* albumin-based nanoparticles) (Figure 1), are versatile vesicles that are attracting attention from the clinic, industry, and laboratory. Appropriately designed nanocarriers can enhance the stability[27], bioavailability[28], and targetability[29] of encapsulated therapeutic agents, which are largely beneficial for treating nervous system diseases. For instance, Liu *et al* [30] designed a quercetin-modified ultrasmall $Cu_{2-x}Se$ antioxidative nanoparticles (CSPQ) to boost Parkinson's disease therapy by activating NRF2. Moreover, previous research on CSPQ by the same authors demonstrated the successful targeting of microglia by coating the nanoparticle with a dopaminergic neuron cell membrane[31]. Gai *et al*[32] prepared folate-modified liposome nanoparticles for the targeted co-delivery of erastin and putative metallothionein (to inhibit NRF2 expression) to enhance the bioavailability and efficiency of the drug/gene combination. These studies demonstrate the potential of nanoparticle drug delivery systems for precise and effective modulation of NRF2 signal pathways.

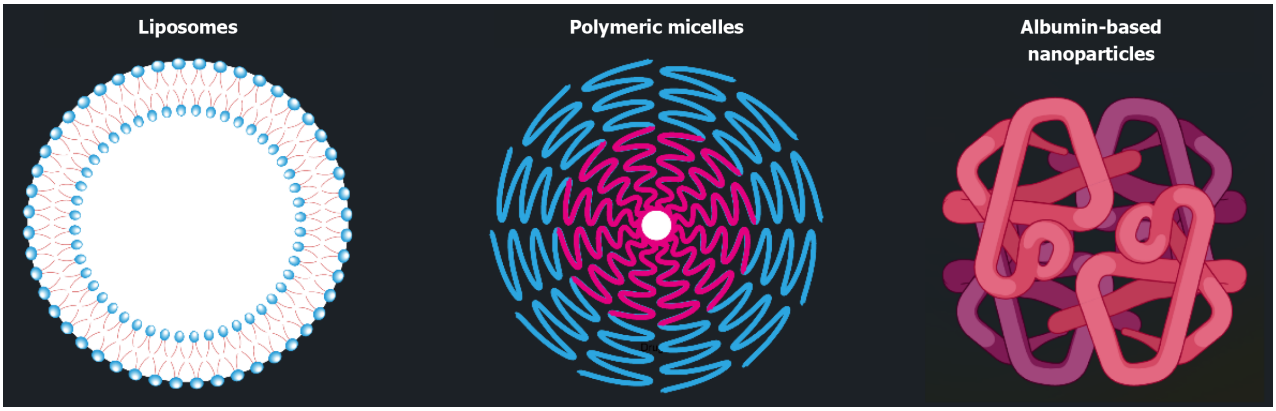

Figure 1 Illustration of representative lipid nanoparticles, polymeric nanoparticles, and protein nanoparticles.

CONCLUSION

We predict that the NRF2 regulation can effectively modulate ferroptosis levels, which are closely associated with nervous system diseases, thereby facilitating the treatment of related disorders. Nanoparticle drug delivery systems are expected to enhance the bioavailability, targetability, and stability of NRF2-related drugs, thereby facilitating the clinical translation of relevant research. In our ongoing studies examining the involvement of NRF2 in a wide range of critical signaling pathways within the human body, we plan to explore the potential of the co-delivery of NRF2-related drugs in combination with other ferroptosis-regulating drugs. We hypothesize that this strategy will enhance cellular drug sensitivity, which exhibits limited efficacy across various tumor cell types. Additionally, NRF2 regulation has demonstrated potential therapeutic efficacy against neurological disorders; however, the treatment of these diseases inevitably encounters delivery challenges such as the blood brain barrier. We envision achieving precise and efficient regulation of NRF2 at specific sites by employing rational bioengineering design strategies for delivery systems, including the utilization of bionic "hitchhiking" mechanisms and charge-mediated penetration capabilities.

FOOTNOTES

Author contributions: Huang YQ was responsible for writing original draft preparation, review, and editing; Huang ZW was responsible for original draft preparation, conceptualization supervision, and funding acquisition; Zhang XJ was responsible for supervision and funding acquisition; all of the authors read and approved the final version of the manuscript to be published.

Supported by The Guangdong Basic and Applied Basic Research Foundation, China, No. 2024A1515011236.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Country of origin: China

ORCID number: Zheng-Wei Huang 0000-0003-2351-7347.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zheng XM

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World Journal of Clinical Cases

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World J Clin Cases 2024 November 26; 12(33): 6660-6663

DOI: 10.12998/wjcc.v12.i33.6660

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Integrating the health belief model into health education programs in a clinical setting

Bee Sung Kam, Sang Yeoup Lee

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Chen YX

Received: June 11, 2024
Revised: September 11, 2024
Accepted: September 19, 2024
Published online: November 26, 2024
Processing time: 107 Days and 5 Hours

Bee Sung Kam, Sang Yeoup Lee, Department of Medical Education, Pusan National University School of Medicine, Yangsan 50612, South Korea

Sang Yeoup Lee, Department of Family Medicine and Biomedical Research Institute, Pusan National University Yangsan Hospital, Yangsan 50612, South Korea

Sang Yeoup Lee, Integrated Research Institute for Natural Ingredients and Functional Foods, Yangsan 50612, South Korea

Corresponding author: Sang Yeoup Lee, MD, PhD, Professor, Department of Family Medicine and Biomedical Research Institute, Pusan National University Yangsan Hospital, Geumo-ro 20, Mulgeum-eup, Yangsan 50612, South Korea. saylee@pnu.edu

Abstract

The article demonstrates that health belief model (HBM)-based health education in hypertensive patients effectively improves blood pressure control and medication adherence at 3 months and 6 months. The HBM addresses perceived barriers, benefits, susceptibility, severity, and self-efficacy, leading to better health behaviors. HBM-based education has been effective in various contexts, including managing chronic diseases, promoting cancer screenings, and preventing infectious diseases. However, the model has limitations, such as cultural applicability and addressing complex health behaviors influenced by environmental factors. Future research should integrate HBM with other theories and conduct longitudinal studies to assess long-term impacts. Despite these limitations, HBM-based education significantly improves patient outcomes, highlighting its potential in health education and promotion when appropriately adapted and implemented. This reinforces the model's value in designing effective health interventions and advancing public health.

Key Words: Health belief model; Hypertension; Health education; Health behavior; Intervention

Core Tip: Improving health outcomes involves boosting patient self-efficacy and highlighting the benefits of healthy behaviors. Additionally, addressing and reducing perceived barriers makes it easier for patients to engage in and maintain healthy behaviors. For a more effective health education framework, utilizing comprehensive interventions that combine the health belief model with other behavioral theories and various educational methods is essential.

Citation: Kam BS, Lee SY. Integrating the health belief model into health education programs in a clinical setting. *World J Clin Cases* 2024; 12(33): 6660-6663
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6660.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6660

TO THE EDITOR

We read the article by Wang *et al*[1] with great interest. The authors implemented health education based on the health belief model (HBM) in hypertensive patients, finding that at 3 months and 6 months, the intervention group had lower systolic and diastolic blood pressures and higher medication adherence compared to the control group. Additionally, perceived barriers were lower, while self-efficacy, perceived benefits, susceptibility, and severity were higher in the intervention group. The initial three months of health education included lectures, brochures, videos, and counseling sessions.

HEALTH EDUCATION CAN EASILY BE NEGLECTED IN A BUSY OUTPATIENT SETTING

While not all patients adhere to health behaviors due to education, it remains an essential intervention for almost all diseases. Some adhere to health behaviors well, but why do others not engage in healthy behaviors despite knowing their benefits? The HBM is used to explain this phenomenon. It was developed by social psychologists at the United States Public Health Service in the 1950s to understand why people do not participate in disease prevention programs or early detection screenings[2]. As Wang *et al*[1] investigated, HBM includes several sub-factors: (1) Perceived susceptibility; (2) Perceived severity; (3) Perceived benefits; (4) Perceived barriers; and (5) Self-efficacy. Perceived susceptibility is the degree to which one feels at risk of a disease, and perceived severity is the perceived seriousness of contracting or leaving a disease untreated. Perceived benefits refer to the perceived advantages of a specific health behavior, and perceived barriers are the perceived obstacles to performing a health behavior. Self-efficacy is the individual's belief in their ability to produce a specific outcome[2]. In short, the HBM posits that cognition plays a crucial role in decision-making, triggering expectations about the outcomes of certain behaviors. People are more likely to engage in health behaviors when they believe they are at high risk for a health issue, the health issue will have severe consequences, the behavior will reduce the risk or severity, the benefits outweigh the barriers, and they have internal or external cues and confidence to perform the behavior. In this context, motivational interviewing, personalized education plans, and digital health tools for reminders and encouragement may be effective strategies for enhancing patient engagement and adherence. Wang *et al*[1] implemented health education based on these principles, resulting in successful outcomes.

The implications of the study by Wang *et al*[1] highlight the significance of structured health education in clinical practice. By utilizing the HBM framework, the study effectively demonstrates how targeted interventions can lead to measurable improvements in health outcomes. For instance, the observed reductions in systolic and diastolic blood pressures among the intervention group underscore the potential for HBM-based education to mitigate cardiovascular risks in hypertensive patients. This finding is particularly relevant in the context of managing chronic conditions, where patient adherence to prescribed health behaviors is critical for long-term disease management. Moreover, the study's approach to reducing perceived barriers while enhancing self-efficacy and perceived benefits is noteworthy. These elements are central to the HBM and play a pivotal role in influencing health behaviors. The intervention's success in these areas suggests that health educators should prioritize these factors when designing educational programs. By addressing patients' perceived barriers and boosting their confidence in managing their health, educators can foster a more proactive approach to disease prevention and management.

Randomized clinical trials using HBM-based interventions have been conducted not only for chronic diseases, cancer screenings, and infectious disease screenings but also to induce lifestyle changes or improve medication adherence in those with diseases. For example, in diabetic patients, the intervention group that received HBM-based education showed significant improvements in metabolic and glycemic profiles compared to the control group[3]. HBM-based education has been demonstrably effective in promoting cancer screenings, including those for colorectal[4], breast[5], oral[6], and cervical cancer[7]. Similarly, it has been utilized for infectious disease prevention education, such as infant screening in human immunodeficiency virus-infected pregnant women[8] or tuberculosis screening[9]. Additionally, it has shown promise in inducing lifestyle changes in patients with non-alcoholic fatty liver disease[10] and hypertension[11]. Furthermore, HBM-based education has been beneficial for improving medication adherence in stroke survivors[12] and tuberculosis patients[13]. It has also proven valuable in preventive approaches, such as secondhand smoke prevention education for pregnant women[14] and human papillomavirus vaccination promotion[15].

The versatility of the HBM in diverse health contexts highlights its broad applicability. However, it is essential to acknowledge the model's limitations to enhance its effectiveness further. Since the HBM was developed in the 1950s within the limited cultural context of the United States, there are concerns about its applicability across different races, societies, and cultures, given the potential differences in beliefs and values. It has also been shown to be less effective for behaviors requiring long-term change influenced by emotional and motivational factors, such as those related to mental health. Moreover, complex health behaviors like smoking or obesity, influenced by environmental, social, and economic factors, may not be adequately addressed by the HBM's focus on individual perceptions and beliefs. Additionally, by placing responsibility on individual perceptions and actions, the HBM may inadvertently promote a culture of blame or stigmatization, negatively impacting individuals. Despite these limitations, appropriate HBM-based educational interventions, as demonstrated by Wang *et al*[1], can positively impact patient outcomes in most clinical situations. This reinforces the model's potential when appropriately adapted and implemented, highlighting its value in health education and promotion. Effective application of HBM to diverse populations requires culturally sensitive education, tailored health messages, trust-building with local leaders, culturally relevant practices, and collaboration with local healthcare providers.

Future research should focus on integrating the HBM with other behavioral theories to address its limitations. For instance, combining the HBM with models emphasizing social and environmental health determinants could provide a more comprehensive framework for designing interventions. While integrating these models is a well-established practice in behavioral science, how they are combined and applied offers potential for new applications. One example is the integration of the HBM with the theory of planned behavior (TPB)[16] and social cognitive theory (SCT)[17]. HBM addresses perceived barriers and benefits, TPB focuses on behavioral intentions, and SCT builds self-efficacy. Thus, the proposed framework would use HBM to address beliefs about health risks and SCT to develop skills and confidence to adopt healthy behaviors. This combined approach could further enhance the effectiveness of health education interventions in clinical settings.

Additionally, the socio-ecological model[18], which considers community, social, and economic factors, may more effectively address the social determinants of health in managing chronic diseases such as hypertension. Furthermore, longitudinal studies are needed to assess the long-term impact of HBM-based education on health behaviors and outcomes, such as behavior change, medication adherence, and blood pressure control. To maintain participant motivation, researchers may implement strategies such as follow-up reminders, real-time data updates, and micro-rewards. Emerging technologies, including wearable devices, virtual reality, artificial intelligence, and online support groups, could provide feedback and foster engagement throughout the study duration. By expanding the evidence base and refining the model, researchers can develop more effective strategies to promote health and prevent disease across diverse populations.

CONCLUSION

The study by Wang *et al*[1] illustrates the practical application of the HBM in improving health outcomes through structured education. While the HBM has limitations, its core principles offer valuable insights into designing effective health interventions. By addressing perceived barriers, enhancing self-efficacy, and highlighting the benefits of health behaviors, educators can motivate patients to adopt and maintain healthier lifestyles. As healthcare continues to evolve, integrating the HBM with other theoretical models and adapting it to various cultural contexts will be crucial for advancing public health and improving patient care.

FOOTNOTES

Author contributions: Kam BS contributed to data collection; Lee SY contributed to article revision; Kam BS and Lee SY contributed to the study design, data analysis, interpretation and wrote the article; all of the authors read and approved the final version of the manuscript to be published.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manscript.

Country of origin: South Korea

ORCID number: Bee Sung Kam 0000-0001-8988-1913; Sang Yeoup Lee 0000-0002-3585-9910.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zheng XM

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