ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 December 16; 12(35): 6754-6863

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 12 Number 35 December 16, 2024

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Retrospective Study

SYSTEMATIC REVIEWS

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 35 December 16, 2024

Contents

CASE REPORT

LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 35 December 16, 2024

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Muhamad Zakaria Brimo Alsaman, MD, Associate Chief Physician, Department of Vascular Surgery, Al-Razi Hospital, Aleppo, Syria; Faculty of Medicine, University of Aleppo, Aleppo 12212, Syria. dr.zakariabrimo@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in PubMed, PubMed Central, *Reference Citation Analysis*, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJCC* as 1.0; JIF without journal self cites: 0.9; 5-year JIF: 1.1; JIF Rank: 168/325 in medicine, general and internal; JIF Quartile: Q3; and 5-year JIF Quartile: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
December 16, 2024

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6754-6759

DOI: 10.12998/wjcc.v12.i35.6754

ISSN 2307-8960 (online)

EDITORIAL

Update on the aetiopathogenesis of obstructive sleep apnea: Role of inflammatory and immune mediated mechanisms

Deb Sanjay Nag, Koshy Varghese, Amlan Swain, Roushan Patel, Seelora Sahu, Merina Sam

Specialty type: Anesthesiology

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D, Grade D

Novelty: Grade C, Grade C

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade C, Grade C

P-Reviewer: Qiang Z; Zhang YD

Received: March 10, 2024

Revised: August 19, 2024

Accepted: September 9, 2024

Published online: December 16, 2024

Processing time: 228 Days and 3.4 Hours

Deb Sanjay Nag, Koshy Varghese, Amlan Swain, Roushan Patel, Seelora Sahu, Merina Sam, Department of Anaesthesiology, Tata Main Hospital, Jamshedpur 831001, Jharkhand, India

Amlan Swain, Roushan Patel, Seelora Sahu, Department of Anaesthesiology, Manipal Tata Medical College, Jamshedpur 831017, India

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

Abstract

Obstructive sleep apnea (OSA) is often a lifestyle disease associated with obesity, which is rapidly evolving as a major health concern with diverse multisystemic implications. To prevent and mitigate its adverse effects and reduce its burden on society, its aetiopathogeneses must be precisely understood. Numerous studies focusing on the range of diverse anatomic, functional, and lifestyle factors have already been carried out to determine the possible contributory roles of these factors in OSA. Recently, evidence to validate the role of inflammatory pathways and immune mechanisms in the aetiopathogeneses of OSA is being developed. This allows for further research and translation of such knowledge for targeted therapeutic and preventive interventions in patients with or who are at risk of developing OSA.

Key Words: Sleep apnea; Obstructive; Polysomnography; Mendelian randomization analysis; Cytokines; C-reactive protein

Core Tip: Although sleep-disordered breathing is any abnormal respiration that occurs during sleep, obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. Its pathogenesis involves a complex interplay of anatomical and functional factors, along with immune cell dysfunction owing to chronic intermittent hypoxia-induced oxidative stress. Thus, to develop specific therapeutic modalities and enhance clinical outcomes in patients with or who are at risk of OSA, these mechanisms must be understood.

Citation: Nag DS, Varghese K, Swain A, Patel R, Sahu S, Sam M. Update on the aetiopathogenesis of obstructive sleep apnea: Role of inflammatory and immune mediated mechanisms. *World J Clin Cases* 2024; 12(35): 6754-6759
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6754.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6754

INTRODUCTION

Sleep-disordered breathing is any abnormal respiration taking place during sleep. Obstructive sleep apnea (OSA), the most common sleep-related breathing disorder, is characterized by recurrent partial or complete obstruction of the upper airway, which results in hypopnea and apnea. This causes sleep fragmentation, intermittent hypoxia, and hypercapnia, which leads to increased sympathetic nervous system activity[1]. Excessive daytime sleepiness in conjunction with OSA is termed OSA syndrome (OSAS)[2].

Comprehensive in-laboratory polysomnography is the gold standard method employed to diagnose sleep-disordered breathing. The apnea–hypopnea index (AHI) is the main outcome utilized to define OSA severity. An airflow reduction of 90% or more for at least 10 s is termed apnea, and the recommended definition of hypopnea is at least 30% airflow reduction for ≥ 10 s with a ≥ 3% decrease in oxygen saturation or arousal. OSA severity based on AHI scores is defined as follows: No OSAS if AHI < 5, mild OSAS if AHI 5–15, moderate OSAS if AHI 15–30, and severe OSAS if AHI > 30[3].

The prevalence of OSA has increased (in developed countries—males 15%, females 5%), and associated morbidity and mortality in adults have been increasing[4,5]. OSA has significant implications for cardiovascular health, neurocognitive function, mental illness, quality of life, and driving safety[6]. OSA is an independent risk factor for hypertension, coronary artery disease, and stroke[7-9]. Moreover, OSA is associated with metabolic syndrome (insulin resistance and type 2 diabetes mellitus), in which adipokines and oxidative stress have been implicated[10,11]. Recent studies revealed that OSA is associated with immune cell dysfunction[12,13]. Furthermore, OSAS has shown an association with cardiovascular disease and cancer[13-15]. Research on how the complicated interaction between inflammatory mediators and immune cells impact the development and severity of OSA is also evolving[13]. Additional genomic association studies in large cohorts can offer additional insights into the role of signal variants in certain specific genes, which may predict their role in affected families[13]. Mendelian randomization has employed epidemiological causality to define the specific impact of the characteristics of the immune cells and their role in OSA[13].

This article aims to elaborate on the aetiopathogenic mechanisms of OSA, especially emphasizing the role of inflammatory and immune-mediated mechanisms.

AETIOPATHOGENESIS

Current evidence

The available evidence reveals that OSA is a multifactorial disease[16]. This current evidence is summarized in Table 1 (Multifactorial causes of OSA).

These factors can be broadly categorized as anatomical and functional factors. The main known cause of OSA is the impaired anatomy of the upper airway. Anatomical causes such as a narrow pharyngeal airway, a longer airway, and certain pharyngeal lumen shapes are all associated with the propensity for pharyngeal collapse during sleep[17].

The functional factors comprise impaired pharyngeal dilator muscle function, premature awakening to mild airway narrowing (low respiratory arousal threshold), and unstable control of breathing[2,15].

On falling asleep, the central respiratory drive and pharyngeal dilator muscle activity in OSA patients is decreased. This along with some degree of upper airway narrowing increases their upper airway resistance. Currently, the balance between the airway forces that tend to close or open the airway tilts unfavorably against the forces that attempt to keep the airway open. This eventually results in partial or complete airway collapse, which leads to hypopnea or total apnea. Based on this, two authors independently searched PubMed databases from inception to January 14, 2024. Furthermore, this review considers the study by Zhao *et al*[13].

EVOLVING EVIDENCE

Role of inflammatory and immune-mediated mechanisms

Activation of inflammatory pathway and systemic inflammatory response: The core of OSA pathogenesis is the regular intermittent hypoxia-induced oxidative stress and formation of superoxide ions. This establishes a chronic proinflammatory state with activation of inflammatory pathways and subsequent endothelial and immune cell dysfunction[18].

The proinflammatory transcription factor, nuclear kappa factor B, and an elevated level of proinflammatory cytokines, including tumour necrosis factor alpha, interleukins 6 (IL-6), and 1 beta (IL-1β), serve as key mediators of inflammation, which, when activated, orchestrate a cascade of the immune response[19,20].

Studies revealed that IL-6 and IL-8 are higher in patients with OSA and correlate with AHI[21,22]. A metanalytic investigation into causal analysis between altered levels of ILs and OSA demonstrated that although most ILs (IL-1β, IL-2,

Table 1 Multifactorial causes of obstructive sleep apnea

Anatomic factors	Nonanatomic factors	Functional factors	Miscellaneous
Micrognathia, retrognathia; facial elongation; mandibular hypoplasia; adenoid and tonsillar hypertrophy; inferior displacement of the hyoid	Central fat distribution; obesity, BMI > 30 kg/m^2; advanced age; male gender; supine sleeping position; pregnancy	Impaired pharyngeal dilator muscle function; low respiratory arousal threshold; unstable control of breathing	Alcohol use; smoking; sedatives and hypnotics use; hereditary

BMI: Body mass index.

IL-4, IL-6, IL-8, IL-12, IL-17, IL-18, and IL-23) increased and IL-10 Levels decreased in OSA, a significant causal relationship could not be found. Interestingly, the same study reported that treatment of OSA lowers IL-1β, IL-6, and IL-8 [23].

Biomarkers of inflammation and OSA: Recent research has shown that OSA is associated with biomarkers of inflammation. The inflammatory biomarkers of interest include C-reactive protein (CRP), fibrinogen, and erythrocyte sedimentation rate (ESR)[24-26]. Combination of these biomarkers has also been studied, which potentially helps to screen and monitor patients with OSA[27]. A study by Elfeky *et al*[27] found that along with comorbidities, ESR, CRP, and systemic inflammatory markers such as SIRI (systemic inflammatory response index) correlate with OSA severity. The positive correlation of SIRI with OSA severity is in agreement with another recent study by Díaz-García *et al*[28], which postulated that activation of inflammasomes is critical in OSA pathophysiology.

Neutrophil lymphocyte ratio and OSA: A meta-analysis that investigated the association of neutrophil lymphocyte ratio (NLR) with OSA revealed that the NLR of patients with OSA is higher than that of controls. The findings of the meta-analysis suggest that NLR is a reliable marker that can be utilized to predict disease progression and detect systemic inflammation in patients with OSA[29]. As both neutrophils and lymphocytes play vital roles in the release of inflammatory mediators, their ratios or absolute counts can indicate the inflammatory status[30]. Moreover, the reduction in the inflammatory markers with continuous-positive airway pressure therapy validates its role in OSA[30].

Immune cell infiltration in OSA: The entry of neutrophils and macrophages into the mucous membrane of the upper airway causes persistent inflammation tissue inflammation, which leads to changes in airway structure. This contributed to the worsening of OSA severity. Recurrent upper respiratory tract infection due to deranged respiratory immunity further exacerbates the upper airway obstruction[31]. Animal studies have shown that intermittent hypoxia increases oxidative stress and decreases antioxidant activity[30]. Nonetheless, to establish causality, further studies are required [30].

Endothelial dysfunction in OSA: Oxidative shear stress to the vascular endothelium results in endothelial dysfunction and vascular remodeling, which contributes to systemic vascular complications and atherosclerosis. These complications, along with the neurohormonal alterations induced by hypoxia-mediated sympathetic overactivity and multiple arousals, cause blood pressure surges resulting in hypertension[32,33]. Cyclical hypoxia in OSA can provoke oxidative stress and adversely impact vascular endothelial function[32].

Adipokine dysregulation in OSA: Adipose tissue serves as a reservoir of immune-modulating adipokines. Dysregulation of adipokines in OSA contributes to systemic inflammation, insulin resistance, and dyslipidemia. Leptin, adiponectin, and other adipokines are involved in immune dysregulation and pathogenesis of OSA-related complications [34].

Circadian rhythm disruption in OSA: Circadian rhythms are 24-h biological clocks that regulate a myriad of physiological processes, such as the sleep–wake cycle, hormone secretion, and metabolism, and modulate the immune response[35-37]. Research is now being directed to analyze differential genes and associated pathways in patients with OSA as well as its effects on immune cell infiltration. The idea is to examine whether regulation of genes related to circadian rhythm could impact disease progression in OSA[38].

Table 2 (Immune cell and obstructive sleep apnea) summarizes the impact of immune cells on OSA, and Table 3 (Inflammatory mediators and obstructive sleep apnea) summarizes the impact of inflammatory mediators.

CONCLUSION

OSA pathogenesis involves a complex interplay of anatomical and functional factors along with immune cell dysfunction caused by chronic intermittent hypoxia-induced oxidative stress. This dysregulation contributes to systemic inflammation, endothelial dysfunction, and metabolic disturbances, exacerbating OSA severity and associated comorbidities. Therefore, these mechanisms must be understood to develop targeted therapies and improve clinical outcomes in OSA patients. To establish the specific role of each inflammatory pathway and immune modulator, further large multicentric trials are needed, to develop specific therapeutic interventions necessary to provide clinically relevant benefits.

Table 2 Immune cell and obstructive sleep apnea

Immune cells	Effect
Monocyte	There were significant alterations in the distribution of monocyte subsets in response to OSAS, characterized by an increase in intermediate and non-classical monocytes and a decrease in classical monocytes[12]
Neutrophils	OSA is independently associated with increased neutrophil counts and inflammation[38]
B-lymphocytes	When B cells are depleted or dysregulated, it can lead to an imbalance in the immune system, potentially resulting in increased inflammation as seen in OSA[38]
T-lymphocytes	There is an imbalance of CD4+ and CD8+ cells in individuals with OSAS, with a high proportion of CD8+ cells and a low proportion of CD4+ cells. These changes are dependent on the AHI[38]
Neutrophil lymphocyte ratio	NLR increases and is directly correlates with AHI[28]

AHI: Apnea–hypopnea index; OSA: Obstructive sleep apnea; NLR: Neutrophil lymphocyte ratio.

Table 3 Inflammatory mediators and obstructive sleep apnea

Inflammatory Mediators	Effect
TNF-α	Elevated levels of inflammatory
IL-6, IL-8, CRP, ESR	Markers correlate with severity of OSA[22,25,38]
Adipokines	
Key adipokines studied include: Leptin, Chemerin, Resistin, Adiponectin, Omentin-1	OSA is associated with elevated levels of leptin, chemerin, and resistin, and decreased levels of adiponectin and omentin-1. These changes may contribute to metabolic dysfunction, inflammation, and cardiovascular risks[38]

TNF-α: Tumour necrosis factor alpha; IL: Interleukin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; OSA: Obstructive sleep apnea.

FOOTNOTES

Author contributions: Nag DS, Varghese K, Swain A, Patel R, Sahu S, Sam M contributed to this paper; Nag DS and Varghese K designed the overall concept and outline of the manuscript; Varghese K, Swain A, Patel R, and Sam M contributed to the discussion and design of the manuscript and review of literature; Nag DS, Varghese K, Swain A, Patel R, Sahu S, and Sam M contributed to the writing and editing of the manuscript; Sahu S, Patel R, and Sam M contributed in the reference indexing and formatting of the manuscript.

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

Country of origin: India

ORCID number: Deb Sanjay Nag 0000-0003-2200-9324; Amlan Swain 0000-0002-0810-7262.

Corresponding Author's Membership in Professional Societies: Indian Society of Anaesthesiology, S2863.

S-Editor: Liu JH
L-Editor: A
P-Editor: Zhang L

REFERENCES

1 **Malhotra A**, White DP. Obstructive sleep apnoea. *Lancet* 2002; **360**: 237-245 [PMID: 12133673 DOI: 10.1016/S0140-6736(02)09464-3]
2 **Spicuzza L**, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. *Ther Adv Chronic Dis* 2015; **6**: 273-285 [PMID: 26336596 DOI: 10.1177/2040622315590318]
3 **Osman AM**, Carter SG, Carberry JC, Eckert DJ. Obstructive sleep apnea: current perspectives. *Nat Sci Sleep* 2018; **10**: 21-34 [PMID: 29416383 DOI: 10.2147/NSS.S124657]
4 **Suri TM**, Ghosh T, Mittal S, Hadda V, Madan K, Mohan A. Systematic review and meta-analysis of the prevalence of obstructive sleep apnea

in Indian adults. *Sleep Med Rev* 2023; **71**: 101829 [PMID: 37517357 DOI: 10.1016/j.smrv.2023.101829]
5 **Lisik D**, Pires GN, Zou D. Perspective: Systematic review and meta-analysis in obstructive sleep apnea - What is lacking? *Sleep Med* 2023; **111**: 54-61 [PMID: 37717377 DOI: 10.1016/j.sleep.2023.09.006]
6 **Yeghiazarians Y**, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, Mehra R, Bozkurt B, Ndumele CE, Somers VK. Obstructive Sleep Apnea and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* 2021; **144**: e56-e67 [PMID: 34148375 DOI: 10.1161/CIR.0000000000000988]
7 **Yuan F**, Zhang S, Liu X, Liu Y. Correlation between obstructive sleep apnea hypopnea syndrome and hypertension: a systematic review and meta-analysis. *Ann Palliat Med* 2021; **10**: 12251-12261 [PMID: 35016417 DOI: 10.21037/apm-21-3302]
8 **Shah NA**, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep Breath* 2010; **14**: 131-136 [PMID: 19777281 DOI: 10.1007/s11325-009-0298-7]
9 **Loke YK**, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2012; **5**: 720-728 [PMID: 22828826 DOI: 10.1161/CIRCOUTCOMES.111.964783]
10 **Xu S**, Wan Y, Xu M, Ming J, Xing Y, An F, Ji Q. The association between obstructive sleep apnea and metabolic syndrome: a systematic review and meta-analysis. *BMC Pulm Med* 2015; **15**: 105 [PMID: 26391008 DOI: 10.1186/s12890-015-0102-3]
11 **Drager LF**, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol* 2013; **62**: 569-576 [PMID: 23770180 DOI: 10.1016/j.jacc.2013.05.045]
12 **Polasky C**, Steffen A, Loyal K, Lange C, Bruchhage KL, Pries R. Redistribution of Monocyte Subsets in Obstructive Sleep Apnea Syndrome Patients Leads to an Imbalanced PD-1/PD-L1 Cross-Talk with CD4/CD8 T Cells. *J Immunol* 2021; **206**: 51-58 [PMID: 33268482 DOI: 10.4049/jimmunol.2001047]
13 **Zhao HH**, Ma Z, Guan DS. Causal role of immune cells in obstructive sleep apnea hypopnea syndrome: Mendelian randomization study. *World J Clin Cases* 2024; **12**: 1227-1234 [PMID: 38524502 DOI: 10.12998/wjcc.v12.i7.1227]
14 **Ge L**, Guyatt G, Tian J, Pan B, Chang Y, Chen Y, Li H, Zhang J, Li Y, Ling J, Yang K. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies. *Sleep Med Rev* 2019; **48**: 101215 [PMID: 31630016 DOI: 10.1016/j.smrv.2019.101215]
15 **Kendzerska T**, Povitz M, Leung RS, Boulos MI, McIsaac DI, Murray BJ, Bryson GL, Talarico R, Hilton JF, Malhotra A, Gershon AS. Obstructive Sleep Apnea and Incident Cancer: A Large Retrospective Multicenter Clinical Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2021; **30**: 295-304 [PMID: 33268490 DOI: 10.1158/1055-9965.EPI-20-0975]
16 **Platon AL**, Stelea CG, Boişteanu O, Patrascanu E, Zetu IN, Roşu SN, Trifan V, Palade DO. An Update on Obstructive Sleep Apnea Syndrome-A Literature Review. *Medicina (Kaunas)* 2023; **59** [PMID: 37629749 DOI: 10.3390/medicina59081459]
17 **Schwab RJ**, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med* 1995; **152**: 1673-1689 [PMID: 7582313 DOI: 10.1164/ajrccm.152.5.7582313]
18 **Ludwig K**, Huppertz T, Radsak M, Gouveris H. Cellular Immune Dysfunction in Obstructive Sleep Apnea. *Front Surg* 2022; **9**: 890377 [PMID: 35874140 DOI: 10.3389/fsurg.2022.890377]
19 **Alberti A**, Sarchielli P, Gallinella E, Floridi A, Floridi A, Mazzotta G, Gallai V. Plasma cytokine levels in patients with obstructive sleep apnea syndrome: a preliminary study. *J Sleep Res* 2003; **12**: 305-311 [PMID: 14633242 DOI: 10.1111/j.1365-2869.2003.00361.x]
20 **Htoo AK**, Greenberg H, Tongia S, Chen G, Henderson T, Wilson D, Liu SF. Activation of nuclear factor kappaB in obstructive sleep apnea: a pathway leading to systemic inflammation. *Sleep Breath* 2006; **10**: 43-50 [PMID: 16491391 DOI: 10.1007/s11325-005-0046-6]
21 **Ciftci TU**, Kokturk O, Bukan N, Bilgihan A. The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. *Cytokine* 2004; **28**: 87-91 [PMID: 15381186 DOI: 10.1016/j.cyto.2004.07.003]
22 **Yokoe T**, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, Hirano T, Adachi M. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 2003; **107**: 1129-1134 [PMID: 12615790 DOI: 10.1161/01.cir.0000052627.99976.18]
23 **Li K**, Wei P, Qin Y, Wei Y. Is C-reactive protein a marker of obstructive sleep apnea?: A meta-analysis. *Medicine (Baltimore)* 2017; **96**: e6850 [PMID: 28489776 DOI: 10.1097/MD.0000000000006850]
24 **Bouloukaki I**, Mermigkis C, Tzanakis N, Kallergis E, Moniaki V, Mauroudi E, Schiza SE. Evaluation of Inflammatory Markers in a Large Sample of Obstructive Sleep Apnea Patients without Comorbidities. *Mediators Inflamm* 2017; **2017**: 4573756 [PMID: 28831208 DOI: 10.1155/2017/4573756]
25 **Lee WH**, Wee JH, Rhee CS, Yoon IY, Kim JW. Erythrocyte sedimentation rate may help predict severity of obstructive sleep apnea. *Sleep Breath* 2016; **20**: 419-424 [PMID: 26315467 DOI: 10.1007/s11325-015-1245-4]
26 **Fleming WE**, Holty JC, Bogan RK, Hwang D, Ferouz-Colborn AS, Budhiraja R, Redline S, Mensah-Osman E, Osman NI, Li Q, Azad A, Podolak S, Samoszuk MK, Cruz AB, Bai Y, Lu J, Riley JS, Southwick PC. Use of blood biomarkers to screen for obstructive sleep apnea. *Nat Sci Sleep* 2018; **10**: 159-167 [PMID: 29942168 DOI: 10.2147/NSS.S164488]
27 **Elfeky SEF**, Ali A, Moazen EM, Alhassoon MH, Elzanaty NA, Alazmi NM, Wu L, Saleh MM. Systemic inflammatory response index as an independent predictor of severity in patients with obstructive sleep apnea. *Egypt J Bronchol* 2024; **18**: 1 [DOI: 10.1186/s43168-023-00253-y]
28 **Díaz-García E**, García-Tovar S, Alfaro E, Jaureguizar A, Casitas R, Sánchez-Sánchez B, Zamarrón E, Fernández-Lahera J, López-Collazo E, Cubillos-Zapata C, García-Río F. Inflammasome Activation: A Keystone of Proinflammatory Response in Obstructive Sleep Apnea. *Am J Respir Crit Care Med* 2022; **205**: 1337-1348 [PMID: 35363597 DOI: 10.1164/rccm.202106-1445OC]
29 **Rha MS**, Kim CH, Yoon JH, Cho HJ. Association between the neutrophil-to-lymphocyte ratio and obstructive sleep apnea: a meta-analysis. *Sci Rep* 2020; **10**: 10862 [PMID: 32616762 DOI: 10.1038/s41598-020-67708-w]
30 **Chen L**, Einbinder E, Zhang Q, Hasday J, Balke CW, Scharf SM. Oxidative stress and left ventricular function with chronic intermittent hypoxia in rats. *Am J Respir Crit Care Med* 2005; **172**: 915-920 [PMID: 15976378 DOI: 10.1164/rccm.200504-560OC]
31 **Shukla SD**, Walters EH, Simpson JL, Keely S, Wark PAB, O'Toole RF, Hansbro PM. Hypoxia-inducible factor and bacterial infections in chronic obstructive pulmonary disease. *Respirology* 2020; **25**: 53-63 [PMID: 31663668 DOI: 10.1111/resp.13722]
32 **Bradley TD**, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 2009; **373**: 82-93 [PMID: 19101028 DOI: 10.1016/S0140-6736(08)61622-0]
33 **Schulz E**, Gori T, Münzel T. Oxidative stress and endothelial dysfunction in hypertension. *Hypertens Res* 2011; **34**: 665-673 [PMID: 21512515

DOI: 10.1038/hr.2011.39]

34 **Tokuda F**, Sando Y, Matsui H, Koike H, Yokoyama T. Serum levels of adipocytokines, adiponectin and leptin, in patients with obstructive sleep apnea syndrome. *Intern Med* 2008; **47**: 1843-1849 [PMID: 18981626 DOI: 10.2169/internalmedicine.47.1035]

35 **Becker-Krail D**, McClung C. Implications of circadian rhythm and stress in addiction vulnerability. *F1000Res* 2016; **5**: 59 [PMID: 26913197 DOI: 10.12688/f1000research.7608.1]

36 **Wang C**, Lutes LK, Barnoud C, Scheiermann C. The circadian immune system. *Sci Immunol* 2022; **7**: eabm2465 [PMID: 35658012 DOI: 10.1126/sciimmunol.abm2465]

37 **Narasimamurthy R**, Hatori M, Nayak SK, Liu F, Panda S, Verma IM. Circadian clock protein cryptochrome regulates the expression of proinflammatory cytokines. *Proc Natl Acad Sci USA* 2012; **109**: 12662-12667 [PMID: 22778400 DOI: 10.1073/pnas.1209965109]

38 **Zhang X**, Wang Y, Pan Z, Hu K. New insights from integrated bioinformatics analysis: the role of circadian rhythm disruption and immune infiltration in obstructive sleep apnea disease. *Front Immunol* 2023; **14**: 1273114 [PMID: 38169659 DOI: 10.3389/fimmu.2023.1273114]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6760-6763

DOI: 10.12998/wjcc.v12.i35.6760

ISSN 2307-8960 (online)

EDITORIAL

Intensive care unit-acquired weakness: Unveiling significant risk factors and preemptive strategies through machine learning

Xiao-Yu He, Yi-Huan Zhao, Qian-Wen Wan, Fu-Shan Tang

Specialty type: Computer science, artificial intelligence

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: Nagamine T

Received: March 18, 2024
Revised: August 22, 2024
Accepted: September 4, 2024
Published online: December 16, 2024
Processing time: 219 Days and 20.4 Hours

Xiao-Yu He, Yi-Huan Zhao, Qian-Wen Wan, Fu-Shan Tang, Department of Clinical Pharmacy, Key Laboratory of Basic Pharmacology of Guizhou Province and School of Pharmacy, Zunyi Medical University, Zunyi 563006, Guizhou Province, China

Corresponding author: Fu-Shan Tang, PhD, Professor, Department of Clinical Pharmacy, Key Laboratory of Basic Pharmacology of Guizhou Province and School of Pharmacy, Zunyi Medical University, No. 6 Xuefu West Road, Xinpu New District, Zunyi 563006, Guizhou Province, China. fstang@vip.163.com

Abstract

This editorial discusses an article recently published in the *World Journal of Clinical Cases*, focusing on risk factors associated with intensive care unit-acquired weakness (ICU-AW). ICU-AW is a serious neuromuscular complication seen in critically ill patients, characterized by muscle dysfunction, weakness, and sensory impairments. Post-discharge, patients may encounter various obstacles impacting their quality of life. The pathogenesis involves intricate changes in muscle and nerve function, potentially leading to significant disabilities. Given its global significance, ICU-AW has become a key research area. The study identified critical risk factors using a multilayer perceptron neural network model, highlighting the impact of intensive care unit stay duration and mechanical ventilation duration on ICU-AW. Recommendations were provided for preventing ICU-AW, emphasizing comprehensive interventions and risk factor mitigation. This editorial stresses the importance of external validation, cross-validation, and model transparency to enhance model reliability. Moreover, the application of machine learning in clinical medicine has demonstrated clear benefits in improving disease understanding and treatment decisions. While machine learning presents opportunities, challenges such as model reliability and data management necessitate thorough validation and ethical considerations. In conclusion, integrating machine learning into healthcare offers significant potential and challenges. Enhancing data management, validating models, and upholding ethical standards are crucial for maximizing the benefits of machine learning in clinical practice.

Key Words: Intensive care unit-acquired weakness; Risk factors; Machine learning; Clinical medicine; Treatment decision

Core Tip: This editorial emphasizes the importance of recognizing the risk factors linked to intensive care unit-acquired weakness and highlights the vital role of machine learning in identifying and managing these factors to improve patient outcomes and enhance the quality of care in clinical settings.

Citation: He XY, Zhao YH, Wan QW, Tang FS. Intensive care unit-acquired weakness: Unveiling significant risk factors and preemptive strategies through machine learning. *World J Clin Cases* 2024; 12(35): 6760-6763
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6760.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6760

INTRODUCTION

Intensive care unit-acquired weakness (ICU-AW) is a debilitating neuromuscular complication that occurs in patients undergoing intensive care treatment in the intensive care unit (ICU)[1]. It is characterized by skeletal muscle dysfunction, leading to various clinical manifestations such as limb muscle weakness, atrophy, diminished deep tendon reflexes, and sensory impairments[2]. Importantly, patients with ICU-AW may also experience a range of challenges after being discharged from the hospital, including physical dysfunction, cognitive impairment, depression, and anxiety disorders [3]. The pathogenesis of ICU-AW is complex and involves intricate functional and structural changes in both muscles and nerves. This condition not only has the potential to result in severe outcomes like tetraplegia or paraplegia but can also lead to long-term disability, significantly impacting the quality of life for patients post-discharge. Given its profound impact on ICU patients, ICU-AW has become a prominent research topic of great interest to scholars worldwide, attracting extensive attention both domestically and internationally[4].

DISCUSSION

An article published by Wang and Long[5] offers a comprehensive exploration of the risk factors associated with ICU-AW. Through the use of a multilayer perceptron neural network model, the study successfully identified critical risk factors for ICU-AW, emphasizing the substantial impact of ICU stay duration and mechanical ventilation duration on its development. These findings provide actionable recommendations for managing these factors to mitigate the risk of ICU-AW within clinical settings. However, it is essential to recognize that the occurrence of ICU-AW is influenced by various other factors, necessitating comprehensive interventions to reduce its incidence. The study's insights serve as valuable reference information for clinicians, aiding in informed decision-making for the prevention and treatment of ICU-AW. It is recommended to further explain the differences between these risk factors identified by machine learning and actual medical practices and to process the data through an iteratively updated machine-learning approach.

While the article demonstrates significant progress in researching ICU-AW risk factors, there are opportunities for improvement in model construction and validation. To enhance the model's robustness, future studies should incorporate external validation[6] to ensure generalizability and employ cross-validation techniques to improve stability and reliability. To avoid the bias that older data may have on machine learning models, it is recommended to group the data by year or time period. This helps to identify the impact of data over different time periods on the model results and to assess the possibility of time bias. Additionally, comparing the multilayer perceptron neural network approach with other common machine learning algorithms would offer valuable insights into its advantages. It is also recommended that researchers share optimal model parameters, make data and model code publicly available, and encourage reproducibility of the study's results.

We propose the following specific recommendations for preventive strategies and interventions regarding ICU-AW. First, the article suggests that reducing the length of ICU stay and duration of mechanical ventilation on ICU-AW effectively lowers the probability of ICU-AW. This finding highlights the significance of early rehabilitation and ventilator withdrawal, offering a new perspective for clinical practice. Second, nutritional interventions and exercise interventions emerge as key strategies for preventing ICU-AW[7]. Nutritional support helps maintain muscle tissue metabolic balance and reduce muscle breakdown, while exercise interventions preserve muscle mass and function through muscle contraction and strength training. The simultaneous implementation of both approaches is expected to yield superior preventive outcomes. Lastly, the application of an early multidisciplinary collaboration in critically ill patient rehabilitation has demonstrated significant achievements. This early multidisciplinary collaboration facilitates close interdisciplinary and cross-disciplinary cooperation, delivering comprehensive and systematic rehabilitation services. Not only does this approach effectively prevent complications like ICU-AW, but it also substantially shortens patients' rehabilitation duration and enhances their daily functioning, muscle strength, and overall, quality of life[8]. This successful practice offers a novel and effective intervention strategy for rehabilitating critically ill patients. Future research is required to determine the extent to which efforts to prevent muscle weakness in the ICU are effective in terms of actual patient prognosis and activities of daily living. The effect of specific strategies such as shortening the duration of mechanical ventilation, early rehabilitation and intervention during deventilation, active nutrition intervention, and even exercise intervention during mechanical ventilation on the prevention of muscle decline in the model should be estimated by machine learning.

All in all, while the article provides valuable insights, it is crucial to enhance the model's stability and reliability through improvements in out-of-sample validation, cross-validation, algorithm comparison, and ensuring transparency in data and code. Moving forward, concrete preventive strategies and interventions for ICU-AW, including reducing ICU stay and mechanical ventilation duration, implementing nutritional and exercise interventions, and promoting early multidisciplinary collaboration in critically ill patient rehabilitation, are recommended. These suggestions provide essential guidance for future clinical practice and research, with the aim of effectively preventing ICU-AW, improving patient recovery outcomes, and enhancing overall quality of life.

CLINICAL APPLICATIONS AND CHALLENGES OF MACHINE LEARNING

In recent years, the utilization of machine learning in clinical medicine has expanded, showcasing its unique advantages. Machine learning provides healthcare professionals with a deeper understanding of disease causation and influencing factors, offering a scientific basis and decision support for clinical treatment. For instance, in colorectal cancer diagnosis, traditional methods face limitations that can be overcome by integrating machine learning with medical imaging, which enables more effective early screening[9]. Machine learning also aids in monitoring aggressive lymphomas and provides critical evidence for cases requiring early intervention[10]. Furthermore, in predicting macrosomia during pregnancy, machine learning empowers healthcare professionals to make more precise risk assessments, facilitating timely interventions for the well-being of both mothers and children[11].

In the realm of clinical pharmacy, machine learning demonstrates significant potential across drug development and clinical implementation. By leveraging drug-target knowledge to train predictive models capable of assessing interactions between new drugs and targets, machine learning offers valuable insights for drug development[12]. Moreover, when constructing predictive models for adverse drug reactions, integrating data from various sources helps reduce the risks associated with such reactions for patients and the healthcare system[13]. Additionally, machine learning-based Clinical Decision Support Systems (CDSSs) play a pivotal role in enhancing patient safety by providing clinicians with clinically valid alerts, improving decision-making processes, and minimizing medication errors[14]. The implementation of CDSS not only ensures patient safety but also enhances the efficiency and reliability of clinical decision-making within healthcare systems.

Despite the widespread application of machine learning, we must address potential challenges. Ensuring the reliability and stability of constructed and validated machine learning models is crucial. Rigorous data set divisions, cross-validation techniques, and other tools are essential to thoroughly evaluate model performance[15]. Efficient collection, processing, and utilization of the increasing volume of clinical data pose another challenge, necessitating the development of robust data processing methods, enhanced data quality management, and reinforced data security measures. Furthermore, legal and ethical issues in the clinical application of machine learning should be addressed through regulatory frameworks, legislative measures, and strengthening the ethical review process[16].

CONCLUSION

In conclusion, while machine learning offers immense potential in clinical medicine and pharmacy, addressing associated challenges is paramount. Through continuous technological advancements, improved data management practices, and ethical reviews, machine learning is poised to play an increasingly vital role in the pharmaceutical sector, contributing significantly to human health. Anticipating further progress in machine learning applications across diverse fields, we look forward to the continued evolution and impact of this technology.

FOOTNOTES

Author contributions: He XY and Zhao YH contributed equally to this work; He XY and Zhao YH contributed to the manuscript outline and composed the initial draft; He XY and Wan QW were responsible for sourcing and organizing the relevant literature; Tang FS and Zhao YH originated the concept for this manuscript; Tang FS provided supervision, reviewed the paper, and finalized the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors have nothing to disclose for this article.

Country of origin: China

ORCID number: Xiao-Yu He 0009-0009-5698-5789; Yi-Huan Zhao 0000-0002-9870-246X; Qian-Wen Wan 0009-0005-3398-0898; Fu-Shan Tang 0000-0001-8779-1041.

S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Wang WB

REFERENCES

1 **Wang W**, Xu C, Ma X, Zhang X, Xie P. Intensive Care Unit-Acquired Weakness: A Review of Recent Progress With a Look Toward the Future. *Front Med (Lausanne)* 2020; **7**: 559789 [PMID: 33330523 DOI: 10.3389/fmed.2020.559789]
2 **Li Z**, Cai Y, Zhang Q, Zhang P, Sun R, Jiang H, Wan J, Wu F, Wang X, Tao X. Intensive care unit acquired weakness: A protocol for an overview of systematic reviews and meta-analysis. *Medicine (Baltimore)* 2020; **99**: e21926 [PMID: 32846861 DOI: 10.1097/MD.0000000000021926]
3 **Zhang W**, Wu J, Gu Q, Gu Y, Zhao Y, Ge X, Sun X, Lian J, Zeng Q. Changes in muscle ultrasound for the diagnosis of intensive care unit acquired weakness in critically ill patients. *Sci Rep* 2021; **11**: 18280 [PMID: 34521934 DOI: 10.1038/s41598-021-97680-y]
4 **Yang Z**, Wang X, Wang F, Peng Z, Fan Y. A systematic review and meta-analysis of risk factors for intensive care unit acquired weakness. *Medicine (Baltimore)* 2022; **101**: e31405 [PMID: 36316900 DOI: 10.1097/MD.0000000000031405]
5 **Wang L**, Long DY. Significant risk factors for intensive care unit-acquired weakness: A processing strategy based on repeated machine learning. *World J Clin Cases* 2024; **12**: 1235-1242 [PMID: 38524515 DOI: 10.12998/wjcc.v12.i7.1235]
6 **Zhang W**, Tang Y, Liu H, Yuan LP, Wang CC, Chen SF, Huang J, Xiao XY. Risk prediction models for intensive care unit-acquired weakness in intensive care unit patients: A systematic review. *PLoS One* 2021; **16**: e0257768 [PMID: 34559850 DOI: 10.1371/journal.pone.0257768]
7 **Heyland DK**, Stapleton RD, Mourtzakis M, Hough CL, Morris P, Deutz NE, Colantuoni E, Day A, Prado CM, Needham DM. Combining nutrition and exercise to optimize survival and recovery from critical illness: Conceptual and methodological issues. *Clin Nutr* 2016; **35**: 1196-1206 [PMID: 26212171 DOI: 10.1016/j.clnu.2015.07.003]
8 **Wang B**, He X, Tian S, Feng C, Feng W, Song L. Influence of Early Multidisciplinary Collaboration on Prevention of ICU-Acquired Weakness in Critically Ill Patients. *Dis Markers* 2022; **2022**: 3823368 [PMID: 35942131 DOI: 10.1155/2022/3823368]
9 **Peng Y**, Deng H. Medical image fusion based on machine learning for health diagnosis and monitoring of colorectal cancer. *BMC Med Imaging* 2024; **24**: 24 [PMID: 38267874 DOI: 10.1186/s12880-024-01207-6]
10 **Bai A**, Si M, Xue P, Qu Y, Jiang Y. Artificial intelligence performance in detecting lymphoma from medical imaging: a systematic review and meta-analysis. *BMC Med Inform Decis Mak* 2024; **24**: 13 [PMID: 38191361 DOI: 10.1186/s12911-023-02397-9]
11 **Shamshuzzoha M**, Islam MM. Early Prediction Model of Macrosomia Using Machine Learning for Clinical Decision Support. *Diagnostics (Basel)* 2023; **13** [PMID: 37685292 DOI: 10.3390/diagnostics13172754]
12 **Xu L**, Ru X, Song R. Application of Machine Learning for Drug-Target Interaction Prediction. *Front Genet* 2021; **12**: 680117 [PMID: 34234813 DOI: 10.3389/fgene.2021.680117]
13 **Nguyen DA**, Nguyen CH, Mamitsuka H. A survey on adverse drug reaction studies: data, tasks and machine learning methods. *Brief Bioinform* 2021; **22**: 164-177 [PMID: 31838499 DOI: 10.1093/bib/bbz140]
14 **Chen CY**, Chen YL, Scholl J, Yang HC, Li YJ. Ability of machine-learning based clinical decision support system to reduce alert fatigue, wrong-drug errors, and alert users about look alike, sound alike medication. *Comput Methods Programs Biomed* 2024; **243**: 107869 [PMID: 37924770 DOI: 10.1016/j.cmpb.2023.107869]
15 **Aittokallio T**. What are the current challenges for machine learning in drug discovery and repurposing? *Expert Opin Drug Discov* 2022; **17**: 423-425 [PMID: 35255749 DOI: 10.1080/17460441.2022.2050694]
16 **Vayena E**, Blasimme A, Cohen IG. Machine learning in medicine: Addressing ethical challenges. *PLoS Med* 2018; **15**: e1002689 [PMID: 30399149 DOI: 10.1371/journal.pmed.1002689]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6764-6769

DOI: 10.12998/wjcc.v12.i35.6764

ISSN 2307-8960 (online)

EDITORIAL

Advancing oral cancer care: Insights from Tongluo Jiedu prescription

Chun-Yao Cheng, Wen-Rui Hao, Ju-Chi Liu, Tzu-Hurng Cheng

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, Grade C, Grade D

Novelty: Grade B, Grade B, Grade C

Creativity or Innovation: Grade B, Grade B, Grade C

Scientific Significance: Grade B, Grade B, Grade C

P-Reviewer: Bao N; Li D; Morya AK

Received: May 15, 2024

Revised: September 2, 2024

Accepted: September 9, 2024

Published online: December 16, 2024

Processing time: 161 Days and 10.5 Hours

Chun-Yao Cheng, Department of Ophthalmology, Cathay General Hospital, Taipei 10633, Taiwan

Chun-Yao Cheng, Department of Medical Education, National Taiwan University Hospital, Taipei 100225, Taiwan

Wen-Rui Hao, Ju-Chi Liu, Division of Cardiology, Department of Internal Medicine, Shuang Ho Hospital, Ministry of Health and Welfare, Taipei Medical University, New Taipei 23561, Taiwan

Wen-Rui Hao, Ju-Chi Liu, Division of Cardiology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11002, Taiwan

Tzu-Hurng Cheng, Department of Biochemistry, School of Medicine, College of Medicine, China Medical University, Taichung 404328, Taiwan

Corresponding author: Tzu-Hurng Cheng, PhD, Professor, Department of Biochemistry, School of Medicine, College of Medicine, China Medical University, No. 91 Xueshi Road, North District, Taichung 404328, Taiwan. thcheng@mail.cmu.edu.tw

Abstract

This editorial highlights the study which investigated the potential of traditional Chinese medicine (TCM) as an adjunctive therapy in oral cancer management. The study included 80 patients with oral cancer to evaluate the effects of the Tongluo Jiedu prescription on inflammatory stress markers, peripheral blood T-cell subsets, and overall immune function. The results indicated that Tongluo Jiedu substantially enhances immune function and reduces oxidative stress, thereby aiding in patient recovery and potentially minimizing treatment-related complications. This editorial discusses the broader implications of these findings for oral cancer care and emphasizes the importance of integrating TCM principles into modern oncology practices.

Key Words: Tongluo Jiedu prescription; Oral cancer patients; Immune function; Oxidative stress; Traditional Chinese medicine; Adjunctive therapy

Core Tip: The study provides valuable insights into the effectiveness of the Tongluo Jiedu prescription as an adjunctive therapy in oral cancer management. By prospectively evaluating immune function and oxidative stress levels in patients with oral cancer receiving Tongluo Jiedu prescription alongside conventional chemotherapy, the study highlighted the potential of traditional Chinese medicine in enhancing patient outcomes. The findings suggest that the Tongluo Jiedu prescription could be a valuable complementary approach to reduce treatment-related complications and accelerate recovery in oral cancer care.

Citation: Cheng CY, Hao WR, Liu JC, Cheng TH. Advancing oral cancer care: Insights from Tongluo Jiedu prescription. *World J Clin Cases* 2024; 12(35): 6764-6769
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6764.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6764

INTRODUCTION

Oral cancer is a major challenge in oncology, adversely affecting patients' health and quality of life. Although advances in conventional therapies such as surgery, chemotherapy, and radiation therapy have been made, managing oral cancer remains challenging owing to high recurrence rates, adverse effects, and treatment-related complications. These challenges highlight the need for complementary therapeutic approaches to enhance outcomes and reduce the treatment burden on patients. Traditional Chinese medicine (TCM) represents one such approach; it offers a holistic treatment philosophy based on centuries-old practices. TCM has gained increasing attention in oncology because of its potential to support conventional cancer therapies by mitigating side effects, enhancing immune function, and reducing oxidative stress, all of which are crucial for improving clinical outcomes. Among the various TCM formulations, the Tongluo Jiedu prescription has demonstrated considerable promise in cancer treatment. Recent studies have reported the diverse benefits of Tongluo Jiedu in cancer care. For example, Hui *et al*[1] demonstrated that Tongluo Jiedu can reduce myocardial fibrosis, a common complication in patients with cancer, by inhibiting the transforming growth factor-β1 (TGF-β1)/Smad2/3 signaling pathway. This finding suggests that Tongluo Jiedu may not only aid in cancer treatment but also protect against cardiovascular complications, thereby enhancing overall patient outcomes. In addition, studies have investigated the effects of Tongluo Jiedu on immune function and oxidative stress in patients with oral cancer and observed substantial improvements. For example, Yin *et al*[2] reported that Tongluo Jiedu modulates immune responses and reduces oxidative stress markers, which are crucial for managing the inflammatory environment associated with cancer. This immunomodulatory effect is particularly vital in oral cancer, where the tumor microenvironment considerably affects disease progression and treatment response. In addition to exploring its direct effects on oral cancer, other studies have examined the broader implications of Tongluo Jiedu in oncology. Zhang *et al*[3] investigated the Jiedu Tongluo Tiaogan Formula, a variant of the Tongluo Jiedu prescription, and determined that it protects pancreatic β cells by inhibiting endoplasmic reticulum stress and excessive autophagy through the calcium/calmodulin-dependent protein kinase kinase beta (CaMKKβ)/ adenosine monophosphate activated protein kinase (AMPK) pathway. Although this study focused on a different cancer type, it highlights the potential systemic benefits of Tongluo Jiedu and its derivatives in managing cancer-related complications. Incorporating Tongluo Jiedu into oral cancer therapy offers a promising approach to enhance patient outcomes. By addressing both the direct effects of cancer and the complications and side effects of conventional treatments, Tongluo Jiedu supports the growing focus on patient-centered care in oncology. This strategy enhances not only treatment effectiveness but also patients' overall quality of life. Although oral cancer poses substantial challenges, incorporating TCM, particularly the Tongluo Jiedu prescription, into treatment regimens can serve as a complementary strategy to enhance therapeutic efficacy and reduce treatment-related burdens. Ongoing research into the mechanisms and benefits of Tongluo Jiedu has indicated its potential as a valuable addition to the multidisciplinary management of oral cancer.

KEY FINDINGS

Yin *et al*[2] conducted a prospective study involving 80 patients with oral cancer to evaluate the effectiveness of the Tongluo Jiedu prescription as an adjunct to conventional chemotherapy. They examined inflammatory stress markers, peripheral blood T-cell subsets, and overall immune function. Their results revealed that patients treated with Tongluo Jiedu exhibited substantial improvements in immune function and a reduction in oxidative stress compared with controls. These findings suggest that Tongluo Jiedu plays a crucial role in counteracting chemotherapy-induced immunosuppression and oxidative stress, which are critical challenges in cancer treatment. The immunomodulatory effects observed in this study are consistent with those noted in other studies on Tongluo Jiedu therapies. For example, Huotan Jiedu Tongluo Decoction, another formulation within this category, has been reported to effectively alleviate myocardial fibrosis, reduce inflammation, and prevent tissue fibrosis[4]. Furthermore, the Jiedu Tongluo Baoshen formula, which can inhibit the phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway in diabetic kidney disease, can protect against cellular stress and damage, indicating the antioxidant property of Tongluo Jiedu[5]. In addition, Zhang *et al*[3] reported that Tongluo Jiedu formulas can protect pancreatic β cells by modulating the CaMKKβ/AMPK pathway, a key player in managing metabolic stress. Although these findings have

been obtained from studies on different health conditions, they collectively demonstrate the broad therapeutic potential of the Tongluo Jiedu prescription in managing oxidative stress and immune dysfunction in various diseases, including cancer. Specifically, the improvements in immune function and the reduction in oxidative stress observed in the study by Yin *et al*[2] add to the growing body of evidence supporting Tongluo Jiedu as a valuable adjunctive therapy in oncology. By enhancing immune response and mitigating oxidative stress, Tongluo Jiedu can substantially improve cancer treatment outcomes and reduce the risk of complications associated with conventional therapies. These findings are consistent with those of other studies that have confirmed the efficacy of Tongluo Jiedu–based therapies in modulating immune function and managing oxidative stress and inflammation in various clinical settings.

ASSESSING LIMITATIONS AND FUTURE DIRECTIONS FOR ENHANCING EFFICACY AND SAFETY OF TONGLUO JIEDU IN CANCER TREATMENT

Although findings related to the Tongluo Jiedu prescription are promising, several critical limitations and future directions must be addressed. These TCM formulations have demonstrated potential in various therapeutic areas, such as inhibiting myocardial fibrosis and enhancing immune function. However, the precise mechanisms through which Tongluo Jiedu exerts its effects, particularly in cancer, remain unclear. A major limitation is the lack of comprehensive mechanistic studies. Although Tongluo Jiedu has been reported to affect TGF-β1/Smad2/3 and CaMKKβ/AMPK pathways, which are relevant in conditions such as myocardial fibrosis and pancreatic β-cell protection, these pathways have not been thoroughly examined in the context of cancer[1,3]. For example, the potential role of Tongluo Jiedu in modulating cancer-related pathways, such as the Akt1-related C-X-C motif chemokine ligand 12/C-X-C chemokine receptor type 4 axis and the sirtuin 1/liver kinase β1/AMPK pathways, requires further exploration[6,7]. These pathways are crucial in regulating cancer cell proliferation, migration, and survival. Understanding how Tongluo Jiedu interacts with these pathways could provide valuable insights into its anticancer potential. Another critical area for further research is the variability in the efficacy of Tongluo Jiedu across different cancer types and stages. Current studies have mainly focused on specific cancers, such as oral and pancreatic cancers, limiting the generalizability of their findings. For instance, although studies have indicated that Tongluo Jiedu can affect immune function and oxidative stress in oral cancer, similar investigations are lacking for other cancer types[2]. This highlights the need for broader clinical trials to evaluate the effectiveness of Tongluo Jiedu across various cancer types. In addition, no study has examined the stage-specific efficacy of Tongluo Jiedu, which is essential for understanding its potential role in early *vs* advanced stages of cancer. Moreover, safety concerns present a substantial challenge. Although preclinical studies have reported that Tongluo Jiedu is generally safe, clinical data on its long-term safety profile, particularly concerning renal and cardiac health, are limited. The potential for adverse interactions with conventional cancer therapies is another area of concern. For example, although Tongluo Jiedu can modulate pathways involved in myocardial fibrosis and pancreatic β-cell protection, these same pathways could interact with cancer therapies in unpredictable ways, leading to therapeutic conflicts[1,3]. Furthermore, the effect of Tongluo Jiedu on the protein kinase RNA-like endoplasmic reticulum kinase-eukaryotic initiation factor 2α–activating transcription factor 4 and autophagy pathways, which are implicated in carotid artery intimal hyperplasia, requires careful monitoring in patients with cancer to prevent unintended complications[8]. To address these limitations, future studies should focus on several key areas. First, in-depth mechanistic studies are necessary to clarify how Tongluo Jiedu interacts with both the known molecular pathways related to cancer and other pathways that may contribute to cancer progression and treatment resistance. Understanding these interactions is crucial for optimizing the integration of Tongluo Jiedu with conventional cancer therapies, potentially enhancing therapeutic outcomes while reducing risks. Second, large-scale, multicenter clinical trials should be conducted to determine the efficacy and safety of Tongluo Jiedu in various types and stages of cancer. These trials should include diverse populations to address variability in treatment responses, which is essential for the broader application of Tongluo Jiedu in cancer care. Additionally, long-term safety monitoring is necessary to track potential adverse effects, particularly in patients with preexisting conditions, such as renal or cardiac diseases. This monitoring can provide valuable insights into any contraindications or necessary adjustments to the formula. Finally, additional studies on the pharmacokinetics and pharmacodynamics of Tongluo Jiedu are essential to determine optimal dosing regimens and minimize adverse effects. These studies can help refine the use of Tongluo Jiedu in clinical settings, ensuring its safe and effective integration into cancer treatment protocols. In summary, although the Tongluo Jiedu prescription is promising as a complementary approach in cancer treatment, substantial challenges remain. Addressing these limitations through rigorous research is crucial to enhance the efficacy and safety of Tongluo Jiedu, ultimately improving outcomes for patients with cancer.

INTEGRATING SUPPORTIVE THERAPIES AND PSYCHOTHERAPY: IMPROVING QUALITY OF LIFE IN CANCER CARE

Patients with cancer experience considerable physical, emotional, and psychological challenges that adversely affect their quality of life. To address these complex challenges, integrating supportive therapies with psychotherapy has become increasingly vital in cancer care. This holistic approach not only targets the physical symptoms of cancer but also addresses the emotional and psychological well-being of patients. Among supportive therapies, TCM formulations such as Tongluo Jiedu have gained prominence for their role in managing cancer-related symptoms and improving patient outcomes. TCM formulations exert anti-inflammatory and immunomodulatory effects, which are particularly beneficial

in mitigating the adverse effects of cancer treatments. For example, Jiedu Tongluo Decoction can ameliorate myocardial fibrosis by inhibiting the TGF-β1/Smad2/3 pathway, rendering it an essential tool in managing cardiac complications associated with cancer therapies[1]. Moreover, these formulations have demonstrated efficacy in modulating immune function and reducing oxidative stress, as evidenced by their use in patients with oral cancer to enhance overall resilience during treatment[2]. For instance, the Tiaogan Formula protects pancreatic β cells by inhibiting endoplasmic reticulum stress and excessive autophagy through the CaMKKβ/AMPK pathway, which could be particularly beneficial for patients with both cancer and diabetes[3]. These findings indicate the potential of TCM not only in managing the primary symptoms of cancer but also in addressing secondary complications that may result from its treatment.

Integrating psychotherapy, particularly cognitive behavioral therapy (CBT), with supportive therapies is a comprehensive approach to cancer care. CBT can effectively alleviate depression and anxiety, which are commonly experienced by patients with cancer and can severely affect their quality of life. For instance, in patients with locoregional advanced nasopharyngeal carcinoma, CBT was reported to considerably improve psychological well-being and reduce adverse emotional reactions to the disease[9]. This finding demonstrates the importance of addressing mental health as a key component of holistic cancer care. Moreover, psychotherapeutic interventions extend beyond traditional talk therapy. Creative modalities, such as art therapy, can reduce fatigue and enhance the quality of life in patients with breast cancer, highlighting the value of integrating diverse therapeutic approaches[10]. This multifaceted strategy not only alleviates physical symptoms but also fosters emotional resilience and a sense of empowerment, which are crucial for the overall well-being of patients with cancer. Integrating supportive therapies, such as Tongluo Jiedu, with psychotherapeutic interventions represents a substantial shift toward a more holistic approach to cancer care. This strategy not only targets the physical aspects of cancer but also addresses the emotional and psychological challenges that are often associated with the disease. By enhancing overall quality of life, this combined approach ensures that cancer care is more patient-centered and comprehensive. As cancer treatment becomes increasingly complex, with more patients living longer, the emphasis on quality of life has become crucial. The integration of supportive therapies and psychotherapy is thus essential to achieving this goal, ensuring that cancer care transcends mere survival to help patients live well despite the disease. Incorporating these therapies into cancer treatment provides a more holistic approach that substantially improves patient outcomes by addressing both the physical and psychological aspects of cancer. As ongoing research continues to validate the effectiveness of these therapies, their role in cancer care is likely to grow, offering hope and a better quality of life to those facing this challenging illness.

DISCUSSION

The integration of TCM principles into modern cancer care represents an evolving approach that complements conventional oncology with holistic strategies. A key example is the Tongluo Jiedu prescription, a traditional remedy designed to target the underlying mechanisms of oral cancer. This prescription aims to enhance the collateral circulation, promote detoxification, and modulate immune function, thus addressing immune suppression and oxidative stress that are often exacerbated by conventional treatments such as chemotherapy and radiation therapy. Yin *et al*[2] provided evidence that incorporating the Tongluo Jiedu prescription into standard chemotherapy regimens considerably enhances immune function and reduces oxidative stress in patients with oral cancer. This enhancement in immune function is particularly crucial because it helps counteract the immunosuppressive effects of both cancer and its treatments. Key components of the prescription, such as *Scutellaria baicalensis* and *Panax ginseng*, increase the activity of natural killer cells, T cells, and macrophages, thereby improving the body's ability to identify and destroy cancer cells. Moreover, the prescription's effectiveness in reducing oxidative stress, a major factor in cancer progression, indicates its therapeutic potential. Oxidative stress results from an imbalance between free radicals and antioxidants, leading to cellular damage. Herbs such as *Astragalus membranaceus* and *Ligusticum chuanxiong*, which are rich in antioxidants, scavenge free radicals, thereby protecting cells from oxidative damage and helping to stabilize the patient's condition by maintaining cellular integrity [2]. These findings are particularly relevant given the challenges posed by chemotherapy-induced immunosuppression and oxidative stress, both of which adversely affect patient outcomes. The ability of Tongluo Jiedu to enhance immune resilience and mitigate oxidative damage suggests its potential as an adjunctive therapy, which can alleviate some of the adverse effects associated with conventional cancer treatments[1]. Additional insights into the prescription's mechanisms reveal its ability to modulate key signaling pathways involved in cancer progression. For example, certain components of Tongluo Jiedu inhibit the PI3K/Akt/mTOR pathway, which drives tumor growth and metastasis. This pathway is commonly upregulated in various cancers, including oral cancer, leading to increased cell proliferation and survival[5]. By targeting the PI3K/Akt/mTOR pathway, Tongluo Jiedu not only impedes tumor growth but also enhances the effectiveness of other therapeutic interventions. In addition, studies on related TCM formulations, such as the Jiedu Tongluo Tiaogan formula, have demonstrated that it protects cells from damage by inhibiting endoplasmic reticulum stress and excessive autophagy through the CaMKKβ/AMPK pathway[3]. These findings suggest the involvement of similar mechanisms in oral cancer, where oxidative stress and inflammation are critical factors in disease progression and treatment resistance. The increasing incidence of chemotherapy-related complications highlights the urgent need for effective therapies with fewer risks. The Tongluo Jiedu prescription offers a promising solution by enhancing immune function and reducing oxidative stress without introducing substantial toxicity. This approach aligns with the evolving focus in oncology on patient-centered care and holistic treatment strategies[8]. From a formulary perspective, the Tongluo Jiedu prescription is carefully developed by combining herbs based on a comprehensive understanding of their individual and synergistic effects. This balanced formulation addresses multiple aspects of cancer pathology, adhering to the TCM principle of restoring bodily balance instead of merely targeting the disease or its symptoms[11]. Overall, the

Tongluo Jiedu prescription represents a comprehensive approach to managing oral cancer; it has the capacity to modulate immune responses, reduce oxidative stress, and affect key signaling pathways. Its integration into modern cancer care not only supports the shift toward more holistic treatment approaches but also holds considerable potential to improve patient outcomes and quality of life. Future research should focus on further elucidating the molecular mechanisms underlying the therapeutic effects of Tongluo Jiedu and exploring its role as a complementary therapy in oral cancer management[2].

CONCLUSION

The study by Yin *et al*[2] represents a pivotal advancement in the exploration of adjuvant therapies for oral cancer, particularly through the use of the Tongluo Jiedu prescription. This study contributes to the growing body of evidence suggesting that Tongluo Jiedu could substantially enhance treatment efficacy for patients with oral cancer. Recent studies, including that by Yin *et al*[2], have highlighted the benefits of Tongluo Jiedu in various medical contexts, further supporting its potential in integrative oncology. Yin *et al*[2] demonstrated that Tongluo Jiedu improves immune function and reduces oxidative stress in patients with oral cancer, addressing immune suppression and oxidative damage that are commonly associated with cancer treatments. These improvements in immune response and oxidative stress are vital for improving overall treatment outcomes and patients' quality of life. In addition, Hui *et al*[1] reported that Tongluo Jiedu can attenuate myocardial fibrosis through the TGF-β1/Smad2/3 pathway, indicating it ability to mitigate fibrotic complications often linked to cancer therapies. Such findings highlight the broader therapeutic potential of Tongluo Jiedu beyond oncology; this thus indicates its ability to manage treatment-related side effects and improve patient resilience. Furthermore, Zhang *et al*[3] elucidated that Tongluo Jiedu can protect cells by inhibiting endoplasmic reticulum stress and excessive autophagy, which are often triggered by aggressive cancer treatments. By modulating key molecular pathways, such as the CaMKKβ/AMPK pathway, Tongluo Jiedu can help reduce the toxicity of conventional cancer therapies, thereby preserving healthy tissues and improving patient outcomes. In conclusion, integrating Tongluo Jiedu with conventional cancer treatments presents a promising approach to enhance therapeutic efficacy while minimizing adverse effects. The ability of Tongluo Jiedu to modulate critical biological pathways, such as the PI3K/Akt/mTOR signaling pathway, as demonstrated by Jin *et al*[5], supports its potential in cancer management by promoting autophagy and reducing tumor growth. This integrative approaches an innovative therapeutic strategy that can improve patient outcomes. However, as with any integrative therapy, closely monitoring patients for potential side effects, such as gastrointestinal discomfort or allergic reactions, is crucial. The safety profile of Tongluo Jiedu must be thoroughly evaluated for different cancer types and stages, and its interactions with other treatments should be carefully considered in clinical practice. Ongoing research and clinical trials are essential to fully realize the benefits of Tongluo Jiedu in oncology, ensuring its safe and effective integration into standard cancer care practices globally.

FOOTNOTES

Author contributions: Cheng CY and Hao WR conceptualized the editorial and provided critical insights into the relevance of the study; Liu JC contributed to the analysis and interpretation of the study's findings; Cheng TH supervised the editorial process and provided overall guidance; all of the authors read and approved the final version of the manuscript to be published.

Conflict-of-interest statement: All authors declare having no conflicts of interest.

Country of origin: Taiwan

ORCID number: Tzu-Hurng Cheng 0000-0002-9155-4169.

S-Editor: Luo ML
L-Editor: A
P-Editor: Wang WB

REFERENCES

1 **Hui J**, Li L, Zhang H, Wang B, Shi J, Song J, Guo J, Li X. Jiedu Tongluo Decoction Attenuates Myocardial Fibrosis through Inhibition of the TGF-β1/Smad2/3 Pathway. *Altern Ther Health Med* 2024; AT9589 [PMID: 39038362]

2 **Yin Y**, Yao Y, Li YJ, Zhao LL, Zhang Q. Effects of Tongluo Jiedu prescription on immune function and oxidative stress in patients with oral cancer. *World J Clin Cases* 2024; **12**: 3045-3052 [PMID: 38898875 DOI: 10.12998/wjcc.v12.i17.3045]

3 **Zhang Q**, Jin W, Wang H, Tang C, Zhao X, Wang Y, Sun L, Piao C. Inhibition of endoplasmic reticulum stress and excessive autophagy by

Jiedu Tongluo Tiaogan Formula *via* a CaMKKβ/AMPK pathway contributes to protect pancreatic β-cells. *J Ethnopharmacol* 2024; **333**: 118440 [PMID: 38885916 DOI: 10.1016/j.jep.2024.118440]

4 **Shen J**, Hu C, Li Y, Shang X, Deng Y, Guo J, Zhang L, Wang J, Zhang W. The Antihypertensive Effects and Mechanisms of Huotan Jiedu Tongluo Decoction in Rats with H-Type Hypertension. *J Vis Exp* 2024 [PMID: 38829134 DOI: 10.3791/65932]

5 **Jin D**, Liu F, Yu M, Zhao Y, Yan G, Xue J, Sun Y, Zhao D, Li X, Qi W, Wang X. Jiedu Tongluo Baoshen formula enhances podocyte autophagy and reduces proteinuria in diabetic kidney disease by inhibiting PI3K/Akt/mTOR signaling pathway. *J Ethnopharmacol* 2022; **293**: 115246 [PMID: 35398500 DOI: 10.1016/j.jep.2022.115246]

6 **Jin D**, Zhao Y, Sun Y, Xue J, Li X, Wang X. Jiedu Tongluo Baoshen formula enhances renal tubular epithelial cell autophagy to prevent renal fibrosis by activating SIRT1/LKB1/AMPK pathway. *Biomed Pharmacother* 2023; **160**: 114340 [PMID: 36738503 DOI: 10.1016/j.biopha.2023.114340]

7 **Ning Y**, Wu Y, Zhou Q, Teng Y. The Effect of Quercetin in the Yishen Tongluo Jiedu Recipe on the Development of Prostate Cancer through the Akt1-related CXCL12/ CXCR4 Pathway. *Comb Chem High Throughput Screen* 2024; **27**: 863-876 [PMID: 37259219 DOI: 10.2174/1386207326666230530095355]

8 **Tian T**, Yu K, Zhang M, Shao X, Chang L, Shi R, Yao B, Deng Y. Huotan Jiedu Tongluo Decoction Inhibits Balloon-Injury-Induced Carotid Artery Intimal Hyperplasia in the Rat through the PERK-eIF2α-ATF4 Pathway and Autophagy Mediation. *Evid Based Complement Alternat Med* 2021; **2021**: 5536237 [PMID: 34335815 DOI: 10.1155/2021/5536237]

9 **Liu F**, Fu SN, Chen YZ, Yan OY, Tong F, Peng WL, Zou R, Wen MN, Jiang L, Ma HZ, He Q, Liu L, Yang H, Huang XF, Han YQ, Wang H, Liu XH. Effects of Cognitive Behavioral Therapy for Depression and Anxiety, Response Rates and Adverse Events in Patients with Locoregional Advanced Nasopharyngeal Carcinoma. *Integr Cancer Ther* 2021; **20**: 15347354211006179 [PMID: 33784875 DOI: 10.1177/15347354211006179]

10 **Joly F**, Pasquier D, Levy C, Mousseau M, D'Almeida MC, Noal S, Le Tinier F, Geffrelot J, Ciais C, Szymczak V, Leon C, Rousselot MP, Darbas S, Hanzen C, Heutte N. Impact of creative art therapy on fatigue and quality of life in patients treated for localized breast cancer: A randomized study. *Psychooncology* 2022; **31**: 1412-1419 [PMID: 35488808 DOI: 10.1002/pon.5940]

11 **Zhao A**, Ma B, Xu L, Yao M, Zhang Y, Xue B, Ren J, Chang D, Liu J. Jiedu Tongluo Granules Ameliorates Post-stroke Depression Rat Model *via* Regulating NMDAR/BDNF Signaling Pathway. *Front Pharmacol* 2021; **12**: 662003 [PMID: 34093193 DOI: 10.3389/fphar.2021.662003]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6770-6774

DOI: 10.12998/wjcc.v12.i35.6770

ISSN 2307-8960 (online)

EDITORIAL

Effects of atrial septal defects on the cardiac conduction system

Jin-Hua Kang, Hong-Yan Wu, Wen-Jie Long

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade C

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade C

P-Reviewer: Chen H; Liu K

Received: July 24, 2024

Revised: August 29, 2024

Accepted: September 12, 2024

Published online: December 16, 2024

Processing time: 92 Days and 6.1 Hours

Jin-Hua Kang, Hong-Yan Wu, Department of Geriatric, Shenzhen Hospital of Shanghai University of Chinese Medicine, Shenzhen 518000, Guangdong Province, China

Wen-Jie Long, Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510006, Guangdong Province, China

Corresponding author: Wen-Jie Long, MD, PhD, Attending Doctor, Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, No. 16 Jichang Road, Guangzhou 510006, Guangdong Province, China. derek1626@163.com

Abstract

The case report presented in this edition by Mu *et al*. The report presents a case of atrial septal defect (ASD) associated with electrocardiographic changes, noting that the crochetage sign resolved after Selective His Bundle Pacing (S-HBP) without requiring surgical closure. The mechanisms behind the appearance and resolution of the crochetage sign remain unclear. The authors observed the disappearance of the crochetage sign post-S-HBP, suggesting a possible correlation between these specific R waves and the cardiac conduction system. This editorial aims to explore various types of ASD and their relationship with the cardiac conduction system, highlighting the diagnostic significance of the crochetage sign in ASD.

Key Words: Atrial septal defects; Cardiac conduction system; Crochetage sign; Electrocardiogram; Selective His bundle pacing

Core Tip: Atrial septal defect (ASD) is characterized by its slow clinical progression, often remaining asymptomatic in children and young adults until diagnosed later in life. Early screening and timely treatment for ASDs are essential. The heightened sensitivity of the crochetage sign in ASDs emphasizes the need for cost-effective, rapid, and non-invasive body surface electrocardiography for early screening, particularly in underserved areas. This editorial seeks to illustrate the impact of ASD on the cardiac conduction system, specifically focusing on the crochetage sign, through a discussion of the recently published case report.

Citation: Kang JH, Wu HY, Long WJ. Effects of atrial septal defects on the cardiac conduction system. *World J Clin Cases* 2024; 12(35): 6770-6774
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6770.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6770

INTRODUCTION

The case report presented in this edition by Mu *et al*[1], highlights the presence of a crochetage sign in atrial septal defect (ASD) potentially associated with the His-Purkinje system within the cardiac conduction system. This editorial reviews the different types of ASDs, their electrocardiographic features, and their relationship to the cardiac conduction system.

ASD is characterized by an underdeveloped or abnormal secondary or primary septum in the atrial septum, creating an abnormal passageway between the left and right atria. This results in atrial-to-horizontal shunts of varying severity and direction. ASD is primarily congenital and represents a common adult congenital heart disease, accounting for approximately 10% of congenital heart diseases and 30% to 40% of adult congenital heart diseases. The occurrence of ASD is more prevalent in females than in males, and there is a noted familial tendency, as first-degree relatives have a relatively high risk ranging from 2% to 6%[2-4]. Although most ASDs are sporadic, genetic syndromes such as Holt-Oram and Ellis van Creveld have shown a genetic association with these atrial defects. Mutations in the *NKX2-5* gene, located on the cardiac homologous chromosome and essential for normal cardiac development, have been linked to autosomal dominant familial ASD and atrioventricular conduction block[5,6].

DIAGNOSIS AND CLASSIFICATION OF ASD

ASD is characterized by slow clinical progression and often remains asymptomatic in children and young adults. Electrocardiograms, cardiac ultrasound, and right heart catheterization are primary methods for diagnosing ASD. As individuals age, symptoms such as exercise intolerance, arrhythmias, right ventricular dysfunction, and pulmonary hypertension become more prevalent. Symptoms like fatigue, shortness of breath, palpitations, and chest tightness may occur, along with manifestations of heart failure, which can lead to a reduced survival rate. The severity of ASD is determined by hemodynamic alterations associated with the size of the defect, left and right ventricular compliance, as well as the resistance within the systemic and pulmonary circulatory systems[7,8]. In instances of considerable left-to-right shunting, an increase in pulmonary blood flow may result in pulmonary congestion along with enlargement of the right atrium and ventricle, attributed to the heightened volume load on the right side of the heart. Sustained high blood flow within the pulmonary circulation can elevate pulmonary artery pressure and lower pulmonary vascular compliance, ultimately leading to persistent pulmonary hypertension. Should the pressure within the right atrium or ventricle surpass that of the left side, the left-to-right shunt may reverse to a right-to-left shunt, leading to symptoms such as cyanosis[7,9,10].

ASD can be classified into four main types: Ostium secundum, ostium primum, sinus venosus, and coronary sinus. The type that occurs most frequently is ostium secundum ASD, comprising 75%-80% of cases, followed by ostium primum ASD (15%-20%), sinus venosus ASD (5%-10%), and the less common coronary sinus defect ASD (< 1%). Primum, sinus venosus, and coronary sinus ASDs often result in significant hemodynamic shunts and may require surgical closure at an early age[11]. ASDs of the ostium secundum type are situated in the atrial septum's central fossa ovalis and can be further classified into central, inferior, superior, and mixed defects. These defects may vary in size and shunt volume over time. The size of the defect, along with the diastolic filling properties or compliance of both the left and right ventricles, influences the direction and volume of blood flow across the ASD[7].

ASD AND CARDIAC CONDUCTION SYSTEM ABNORMALITIES

ASD is a congenital heart condition characterized by structural abnormalities in the heart chambers that disrupt the normal positioning of the heart's electrical conduction system. Typically, the right ventricle and right bundle branch are affected, leading to abnormal electrocardiograms, such as conduction blocks. Secundum ASDs, usually located higher in the heart, primarily impact the interjunctional bundles. Over time, these changes can also affect the His-Purkinje system, resulting in right axis deviation and incomplete right bundle branch block[12]. In contrast, ostium primum ASDs are located in the lower section of the atrial septum and can exhibit a left axis deviation. They can cause delays in signal transmission to the atrioventricular (AV) node due to involvement of the anterior mitral leaflet cleft or tricuspid septal cleft[13]. Sinus venosus ASDs may exhibit atrial ectopic pacing and P-wave inversion in leads II, III, and aVF, suggesting sinus node abnormalities[14,15]. If ASDs involving the coronary sinus extend to the opening area of the coronary sinus, the position of the AV node may shift posteriorly, potentially leading to conduction disturbances[16]. These pathological changes may result from developmental disorders and structural abnormalities in the conduction system caused by ASDs, as well as hemodynamic abnormalities in the septum and central fibrous body[17].

Due to the mild early symptoms and subtle signs of the disease, many patients may not recognize the need for timely treatment. Early diagnosis and prompt atrial septal repair are crucial for improving patient outcomes. Thus, there is a critical need for early screening and diagnostic markers for atrial septal defects. Cardiac ultrasound is essential for

diagnosing ASD as it offers vital details regarding the size and location of the defect, the direction of shunting, and dilation of the right heart, as well as diastolic septal inversion indicating hemodynamic significance. Additionally, cost-effective and accessible body surface electrocardiography plays a vital role in early screening.

ASD AND CROCHETAGE SIGN

Electrocardiograms of patients with ASDs often display various abnormalities, including incomplete or complete right bundle branch block, prolonged PR interval, atrioventricular block, atrial arrhythmia, right atrial and right ventricular hypertrophy, and right deviation of the frontal electrical axis. However, electrocardiography alone is not sufficiently sensitive or specific for diagnosing ASDs. In 1959, Rodriguez-Alvarez *et al*[18] observed tangential tracings on the apical part of the QRS wave cluster in 11 patients with ASDs, introducing the concept of the Crochetage R wave, though it initially received little attention. Since Heller's description of the Crochetage R wave as a distinctive electrocardiography (ECG) diagnostic marker for ASD, this feature has gained recognition among clinicians. The Crochetage R wave is characterized by a notch in the ascending branch or apex of the R wave in the inferior wall leads, typically appearing within 80 ms following the initiation of the QRS complex and creating a distinctive M-shaped pattern in the ascending branch or apex of the R wave[19]. The Crochetage sign in leads II, III, and aVF has a sensitivity of 57% and a specificity of 92% for diagnosing ASD[12]. These Crochetage R waves can manifest in a single inferior wall lead or in 2-3 inferior wall leads simultaneously. Sensitivity and specificity are particularly high when Crochetage R waves are present in all three inferior wall leads or in conjunction with incomplete right bundle branch block. After the surgical repair of ASDs, R-wave patterns frequently occur before the pattern of incomplete right bundle branch block fades in 35% of individuals[19,20]. Furthermore, the presence of the Crochetage sign is significantly correlated with ASD diameter and defect area, with patients exhibiting these waves often having larger defect areas compared to those without[12,21].

S-HBP AND THE DISAPPEARANCE OF CROCHETAGE SIGN

Due to the patient's ASD, who developed heart failure and exhibited atrial fibrillation witha risk of prolonged R-R interval, second-degree atrioventricular block, and incomplete right bundle branch block, selective His bundle pacing (S-HBP) was performed as a preliminary intervention. Currently, His bundle pacing (HBP) is considered the most physiological method for pacing, since it achieves synchronization of ventricular excitation by directly stimulating the His bundle. This stimulation ensures that the heart's electrical activity is predominantly conducted through the His-Purkinje fiber system, facilitating synchronized biventricular contractions. In certain patients with conduction abnormalities, HBP can correct established conduction issues[22,23]. There are two types of HBP: S-HBP and non-selective His bundle pacing (NS-HBP). S-HBP differs from NS-HBP in that while NS-HBP captures both the right and left portions of the His bundle and the membranous septal ventricular muscle simultaneously through high-output pacing, S-HBP operates at a lower threshold than that of the peripheral ventricular myocardium. By using low-output pacing, S-HBP eliminates the involvement of the membranous septal ventricular muscle, correcting the block solely by stimulating either the right or left aspect of the His bundle[23].

Considering the potential risks associated with implanting an atrial septal occluder device, which could further impact the cardiac conduction system, the attending physician opted for S-HBP as the initial treatment approach. Following this procedure, the postoperative surface electrocardiogram showed the disappearance of the crochetage sign. The mechanism underlying the crochetage sign in ASDs remains unclear. However, most scholars suggest it may be related to excessive cardiac pressure and volume load, as well as the anatomical changes observed in individuals diagnosed with ASD. The resolution of the crochetage sign indicates improved patient prognosis and a reduction in symptoms. S-HBP has the potential to enhance synchronized ventricular contraction, correct hemodynamics, alleviate cardiac pressure and volume load, and restore the functionality of the cardiac conduction system in ASD patients. Thus, the implementation of S-HBP may lead to the resolution of the crochetage sign, accompanied by a reduction in patient symptoms and an improvement in long-term prognosis. The late follow-up of the disappearance of the crochetage sign after S-HBP, as reported by Mu *et al*[1], supports this hypothesis. Nevertheless, additional studies on the effects of S-HBP on ASD are still needed.

CONCLUSION

Early screening for ASDs is crucial, along with subsequent treatment. The high sensitivity of the crochetage sign in ASDs highlights the importance of using cost-effective, rapid, and non-invasive body surface ECG for early screening, particularly in disadvantaged areas. However, it is important to note that the crochetage sign may yield false positives and has limitations in assessing the specific type of defect in patients with ASD. Therefore, a definitive diagnosis and accurate classification of ASD require further clarification through additional modalities, such as echocardiography. Moreover, the application of S-HBP in ASD patients who have experienced cardiac conduction blockages and congestive heart failure has the potential to significantly benefit many individuals with ASDs, improving their quality of life, functional status, and overall survival. Further research is warranted to explore the direct relationship between the presence and resolution of the crochetage sign in ASDs and cardiac conduction disorders.

FOOTNOTES

Author contributions: Long WJ conceived the idea; Kang JH and Wu HY conducted a literature search; Kang JH wrote the preliminary draft; Long WJ and Wu HY critically reviewed as well as improved the manuscript; all authors have read and approved the final manuscript.

Supported by Guangzhou Municipal Science and Technology Bureau's 2024 Basic and Applied Basic Research Topic, China, No. 2024A04J4491, and No. 2024A04J4254; the Scientific Research Project of Guangdong Provincial Bureau of Traditional Chinese Medicine, China, No. 2022ZYYJ01; and the Soft Science Research Program of Luohu District, Shenzhen, China, No. LX202402016.

Conflict-of-interest statement: There are no conflict-of-interest disclosures by any authors.

Country of origin: China

ORCID number: Wen-Jie Long 0000-0002-9849-5077.

S-Editor: Liu JH
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Mu YG**, Liu KS. Selective his bundle pacing eliminates crochetage sign: A case report. *World J Clin Cases* 2024; **12**: 5276-5282 [PMID: 39109045 DOI: 10.12998/wjcc.v12.i22.5276]
2 **Moore J**, Hegde S, El-Said H, Beekman R 3rd, Benson L, Bergersen L, Holzer R, Jenkins K, Ringel R, Rome J, Vincent R, Martin G; ACC IMPACT Steering Committee. Transcatheter device closure of atrial septal defects: a safety review. *JACC Cardiovasc Interv* 2013; **6**: 433-442 [PMID: 23702008 DOI: 10.1016/j.jcin.2013.02.005]
3 **Tobis J**, Shenoda M. Percutaneous treatment of patent foramen ovale and atrial septal defects. *J Am Coll Cardiol* 2012; **60**: 1722-1732 [PMID: 23040567 DOI: 10.1016/j.jacc.2012.01.086]
4 **Botto LD**, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. *Pediatrics* 2001; **107**: E32 [PMID: 11230613 DOI: 10.1542/peds.107.3.e32]
5 **Liu XY**, Wang J, Yang YQ, Zhang YY, Chen XZ, Zhang W, Wang XZ, Zheng JH, Chen YH. Novel NKX2-5 mutations in patients with familial atrial septal defects. *Pediatr Cardiol* 2011; **32**: 193-201 [PMID: 21188375 DOI: 10.1007/s00246-010-9859-6]
6 **Elliott DA**, Kirk EP, Yeoh T, Chandar S, McKenzie F, Taylor P, Grossfeld P, Fatkin D, Jones O, Hayes P, Feneley M, Harvey RP. Cardiac homeobox gene NKX2-5 mutations and congenital heart disease: associations with atrial septal defect and hypoplastic left heart syndrome. *J Am Coll Cardiol* 2003; **41**: 2072-2076 [PMID: 12798584 DOI: 10.1016/s0735-1097(03)00420-0]
7 **Brida M**, Chessa M, Celermajer D, Li W, Geva T, Khairy P, Griselli M, Baumgartner H, Gatzoulis MA. Atrial septal defect in adulthood: a new paradigm for congenital heart disease. *Eur Heart J* 2022; **43**: 2660-2671 [PMID: 34535989 DOI: 10.1093/eurheartj/ehab646]
8 **Geva T**, Martins JD, Wald RM. Atrial septal defects. *Lancet* 2014; **383**: 1921-1932 [PMID: 24725467 DOI: 10.1016/S0140-6736(13)62145-5]
9 **Engelfriet PM**, Duffels MG, Möller T, Boersma E, Tijssen JG, Thaulow E, Gatzoulis MA, Mulder BJ. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. *Heart* 2007; **93**: 682-687 [PMID: 17164490 DOI: 10.1136/hrt.2006.098848]
10 **Craig RJ**, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation* 1968; **37**: 805-815 [PMID: 5646864 DOI: 10.1161/01.cir.37.5.805]
11 **Tadros VX**, Asgar AW. Atrial septal defect closure with left ventricular dysfunction. *EuroIntervention* 2016; **12** Suppl X: X13-X17 [PMID: 27174105 DOI: 10.4244/EIJV12SXA3]
12 **Bayar N**, Arslan Ş, Köklü E, Cagirci G, Cay S, Erkal Z, Ayoglu RU, Küçükseymen S. The importance of electrocardiographic findings in the diagnosis of atrial septal defect. *Kardiol Pol* 2015; **73**: 331-336 [PMID: 25563473 DOI: 10.5603/KP.a2014.0240]
13 **Fournier A**, Young ML, Garcia OL, Tamer DF, Wolff GS. Electrophysiologic cardiac function before and after surgery in children with atrioventricular canal. *Am J Cardiol* 1986; **57**: 1137-1141 [PMID: 3706166 DOI: 10.1016/0002-9149(86)90688-0]
14 **Attenhofer Jost CH**, Connolly HM, Danielson GK, Bailey KR, Schaff HV, Shen WK, Warnes CA, Seward JB, Puga FJ, Tajik AJ. Sinus venosus atrial septal defect: long-term postoperative outcome for 115 patients. *Circulation* 2005; **112**: 1953-1958 [PMID: 16172274 DOI: 10.1161/CIRCULATIONAHA.104.493775]
15 **Davia JE**, Cheitlin MD, Bedynek JL. Sinus venosus atrial septal defect: analysis of fifty cases. *Am Heart J* 1973; **85**: 177-185 [PMID: 4569755 DOI: 10.1016/0002-8703(73)90458-4]
16 **Webb G**, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. *Circulation* 2006; **114**: 1645-1653 [PMID: 17030704 DOI: 10.1161/CIRCULATIONAHA.105.592055]
17 **Bolens M**, Friedli B. Sinus node function and conduction system before and after surgery for secundum atrial septal defect: an electrophysiologic study. *Am J Cardiol* 1984; **53**: 1415-1420 [PMID: 6720586 DOI: 10.1016/s0002-9149(84)90825-7]
18 **Rodriguez-Alvarez A**, Martinez DE Rodriguez G, Goggans AM, Holsapple CK, Etier EL, Marietta JS, Wilson SW, Kelly GB. The vectorcardiographic equivalent of the "crochetage" of the QRS of the electrocardiogram in atrial septal defect of the ostium secundum type.

Preliminary report. *Am Heart J* 1959; **58**: 388-394 [PMID: 14438235 DOI: 10.1016/0002-8703(59)90155-3]

19 **Heller J**, Hagège AA, Besse B, Desnos M, Marie FN, Guerot C. "Crochetage" (notch) on R wave in inferior limb leads: a new independent electrocardiographic sign of atrial septal defect. *J Am Coll Cardiol* 1996; **27**: 877-882 [PMID: 8613618 DOI: 10.1016/0735-1097(95)00554-4]

20 **Cohen JS**, Patton DJ, Giuffre RM. The crochetage pattern in electrocardiograms of pediatric atrial septal defect patients. *Can J Cardiol* 2000; **16**: 1241-1247 [PMID: 11064298]

21 **Shen L**, Liu J, Li JK, Xu M, Yuan L, Zhang GQ, Wang JY, Huang YJ. The Significance of Crochetage on the R wave of an Electrocardiogram for the Early Diagnosis of Pediatric Secundum Atrial Septal Defect. *Pediatr Cardiol* 2018; **39**: 1031-1035 [PMID: 29564520 DOI: 10.1007/s00246-018-1857-0]

22 **Burri H**, Jastrzebski M, Cano Ó, Čurila K, de Pooter J, Huang W, Israel C, Joza J, Romero J, Vernooy K, Vijayaraman P, Whinnett Z, Zanon F. EHRA clinical consensus statement on conduction system pacing implantation: endorsed by the Asia Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS), and Latin American Heart Rhythm Society (LAHRS). *Europace* 2023; **25**: 1208-1236 [PMID: 37061848 DOI: 10.1093/europace/euad043]

23 **Curila K**, Prochazkova R, Jurak P, Jastrzebski M, Halamek J, Moskal P, Stros P, Vesela J, Waldauf P, Viscor I, Plesinger F, Sussenbek O, Herman D, Osmancik P, Smisek R, Leinveber P, Czarnecka D, Widimsky P. Both selective and nonselective His bundle, but not myocardial, pacing preserve ventricular electrical synchrony assessed by ultra-high-frequency ECG. *Heart Rhythm* 2020; **17**: 607-614 [PMID: 31805370 DOI: 10.1016/j.hrthm.2019.11.016]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6775-6781

DOI: 10.12998/wjcc.v12.i35.6775

ISSN 2307-8960 (online)

EDITORIAL

Periodontitis and chronic kidney disease: A bidirectional relationship based on inflammation and oxidative stress

Melissa Martínez Nieto, Martha Leticia De Leon Rodríguez, Rocio del Carmen Anaya Macias, Sarah Monserrat Lomelí Martínez

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 C

P-Reviewer: Coronel-Zubiate FT

Received: July 24, 2024
Revised: August 29, 2024
Accepted: September 9, 2024
Published online: December 16, 2024
Processing time: 91 Days and 20.4 Hours

Melissa Martínez Nieto, Independent Researcher, Tijuana 22116, Baja California, Mexico

Martha Leticia De Leon Rodríguez, Rocio del Carmen Anaya Macias, Department of Medical and Life Sciences, Centro Universitario de la Ciénega, Centro Universitario de la Ciénega, Universidad de Guadalajara, Ocotlan 47810, Jalisco, Mexico

Sarah Monserrat Lomelí Martínez, Department of Medical and Life Sciences, Centro Universitario de la Ciénega, Universidad de Guadalajara, Ocotlán 47810, Mexico

Sarah Monserrat Lomelí Martínez, Master of Public Health, Department of Well-being and Sustainable Development, Centro Universitario del Norte, Universidad de Guadalajara, Colotlan 46200, Jalisco, Mexico

Corresponding author: Sarah Monserrat Lomelí Martínez, MSc, PhD, Academic Research, Adjunct Associate Professor, Professor, Department of Medical and Life Sciences, Centro Universitario de la Ciénega, Universidad de Guadalajara, Av. Universidad 1115, Col. Lindavista, Ocotlán 47810, Mexico. sarah.lomeli@academicos.udg.mx

Abstract

Chronic kidney disease (CKD) and chronic periodontitis (CP) are prevalent conditions which significantly impact public health worldwide. Both diseases share inflammatory and oxidative stress mechanisms, an indication of a likely bidirectional relationship. This editorial explored the association between CKD and CP by highlighting common inflammatory mechanisms and recent research findings that address this interrelationship. Through reviews of recent studies, we discussed how periodontal bacteria may activate systemic immune responses that affect both periodontal and renal tissues. Additionally, meta-analysis data indicated an increased risk of CKD development in patients with CP, and vice versa. The results suggest the need for more rigorous research in the future in order to address the confounding factors and evaluate specific periodontal health interventions and their direct effects on kidney function. We emphasized the importance of comprehensive and multidisciplinary care for the improvement of the overall health of patients affected by CP and CKD.

Key Words: Periodontitis; Chronic kidney disease; Periodontal disease; Oxidative stress; Inflammation

Core Tip: In this editorial, we reviewed the recent meta-analysis by Yang *et al*, which investigated the association between chronic periodontitis (CP) and chronic kidney disease (CKD). The analysis showed that CP patients have increased risk of CKD, and vice versa. This review also incorporated findings from other significant studies that support this link. We highlighted the need for more consistent definitions, rigorous adjustment for confounding factors, and well-designed prospective studies to ascertain the causal relationship between CP and CKD. This ongoing investigation is crucial for enhancing the management of periodontal health of CKD patients and for improving overall patient outcomes.

Citation: Martínez Nieto M, De Leon Rodríguez ML, Anaya Macias RDC, Lomelí Martínez SM. Periodontitis and chronic kidney disease: A bidirectional relationship based on inflammation and oxidative stress. *World J Clin Cases* 2024; 12(35): 6775-6781
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6775.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6775

INTRODUCTION

Chronic kidney disease (CKD) presents a global public health problem. The Clinical Practice Guideline for the evaluation and management of chronic kidney disease (KDIGO) has estimated that currently, approximately 9.1% of the global population has this condition in one clinical stage or the other[1,2]. The World Health Organization (WHO) has stated that CKD is the fourteenth leading cause of death worldwide[3,4]. Moreover, WHO has projected that CKD may become the fifth leading cause of death by 2040[3,5]. This is due to the high morbidity and mortality associated with cardiovascular diseases, severe infections, diabetes mellitus, among others, which generate high treatment costs[4,6,7]. In the United States, it has been estimated that approximately 64 million dollars are spent each year as treatment costs. However, not much is known on he related expenditure costs in Latin American countries[2,7]. Therefore, the identification of patients at high risk of developing CKD, as well as implementation of timely diagnosis and treatment, are of high health priority[1,8]. CKD is defined as kidney function failure or structural failure for a minimum of 3 months, with health implications accompanied by a decrease in the glomerular filtration rate (GFR) below 90 mL/min/L/1.73 m². It is classified into 5 stages based on GFR and albuminuria category of the KDIGO 2024[7]. There are multiple causes of CKD. These causes are diabetes mellitus, obesity, dyslipidemia, hypertension, chronic inflammatory states, autoimmune diseases, and smoking, in addition to other factors[3,5,8,9]. However, regardless of the cause, CKD affects multiple processes which under normal conditions, maintain systemic homeostasis. As the GFR decreases, there are more imbalances in other organs and systems[3]. Most of the imbalances involve elevation of nitrogenous wastes, hematological and immunological disorders; changes in acid-base balance and body water distribution; electrolyte disorders affecting potassium, calcium and magnesium, and failure of the renin-angiotensin-aldosterone system[10]. Moreover, the elevation of inflammatory markers such as IL1 and C-reactive protein in CKD patients are potent predictors of development of atherosclerotic vascular disease and infectious processes, which significantly increase mortality in these patients[3].

Periodontitis is a highly prevalent disease which affects approximately 50% of the general population[1,9], and it is the sixth most prevalent dental disease worldwide[5,11,12]. A previous estimate indicated that at least 743 million people worldwide were affected by periodontitis. However, over the last 30 years, up to 99% increase in prevalence of periodontitis has been observed, especially in developing countries[1]. This makes it an epidemiologically relevant condition [13]. Chronic periodontitis (CP) is an inflammatory infection that affects the supporting tissues of the teeth, *i.e.*, the gums, cementum, alveolar bone, and periodontal ligament. The development and maturation of dental biofilm consisting of bacterial colonies on the teeth, is the primary etiological factor that contributes to the pathogenesis of periodontal disease [1,14]. Some biomarkers associated with the inflammatory processes observed in CP are C-reactive protein, tumor necrosis factor-alpha, interleukin-6, and interleukin-1 beta[3,15].

Multiple studies have demonstrated the relationship amongst periodontitis, various systemic conditions such as diabetes mellitus, pregnancy and CKD[7]. In all cases, it was determined that the association is governed by systemic immunoinflammatory reactions in patients with periodontitis[3,11,14], especially in those with severe stages of the disease. This suggests a direct relationship between the severity of CP and the progression of CKD, with the worsening of one disease potentially exacerbating the other[7,10,16].

The objective of this editorial was to study the association between CP and CKD, thereby highlighting common inflammatory mechanisms and recent research findings that address this interrelationship. In doing so, we hoped to emphasize the importance of comprehensive and multidisciplinary care in improving the overall health of patients affected by the two diseases.

ASSOCIATION BETWEEN CHRONIC KIDNEY DISEASE AND PERIODONTAL DISEASE

Although CP and CKD have various causes, recent studies have demonstrated a bidirectional association between the two conditions[2,5,11,17]. Clinical trials suggest higher incidence and severity of periodontal problems in CKD patients, with figures ranging from 75% to 90% in different studies[3]. Cross-sectional studies have shown that advanced CP increases the risk of CKD in stages 4 and 5 up to 3.9 folds[7,9]. A cohort study on a large number of CKD patients demonstrated that the risk of mortality was increased by 32%-41% when the patients also had periodontitis[10,18]. In a meta-analysis on 17 studies, a relationship between CKD and periodontitis was observed with an odds ratio (OR) of 1.49 to 2.39, which tended to increase in cases of severe periodontitis[5,8].

In another comparative study on 66 periodontal disease patients, 33 of whom had pre-dialysis CKD, while 33 had no renal disease, all subjects received non-surgical periodontal treatment. Serum inflammatory markers were measured before and after periodontal treatment. It was found that patients with periodontitis and CKD had significantly higher levels of these parameters than patients without CKD before receiving non-surgical treatment ($P < 0.05$). However, six weeks after non-surgical management, there were significant reductions in levels of inflammatory markers ($P < 0.05$), thereby demonstrating the importance of maintaining adequate periodontal health in these patients[3,19].

Various mechanisms have been described in the association of these conditions. These mechanisms include the migration of bacteria from periodontal pockets along with cytokines and pro-inflammatory factors and lipopolysaccharides that cause endothelial damage, resulting in a persistent systemic inflammatory state. This favors the development of hypertension and cardiovascular diseases which are significant risk factors for CKD and renal endothelial damage[5,20]. Additionally, the systemic inflammatory state promotes insulin resistance which leads to the onset or worsening of diabetes mellitus[9,21], another disease that may cause CKD. Changes in CKD, such as increased serum urea and changes in salivary pH, modify the oral microbiota and increase the risk of pathogenic bacterial colonization[5,10,17].

The exacerbated inflammatory state caused by both diseases leads to a significant imbalance in oxidative stress response at the systemic level, with increased generation of reactive oxygen species (ROS)[15,21], and a decrease in glutathione peroxidase, a key antioxidant and a potent enzyme involved in regulating oxidative stress. This enzyme is produced mainly in the kidney, but it is also found in other structures, including periodontal tissues. A comparative study amongst four groups (healthy, periodontitis, CKD without periodontitis, and CKD with periodontitis) measured serum glutathione peroxidase levels, and it was observed that patients with CP had the highest levels of this enzyme, while those with CKD and CP had reduced levels, which may be associated with multiple causes[22] (Figure 1). However, the study is inconclusive.

Several studies on the connection between PD and CKD have been carried out by focusing on inflammation and oxidative stress as key mechanisms. These connections are particularly relevant in patients with underlying conditions like diabetes and hypertension.

Shinjo *et al*[23] reported that hyperglycemia, hyperlipidemia, chronic inflammation, and impaired insulin function are crucial factors in the progression of periodontitis in individuals with diabetes. The relationship between hyperglycemia and oxidative stress is particularly significant, as elevated glucose levels in people with diabetes may damage pancreatic β-cells, leading to insulin deficiency and chronic hyperglycemia, which in turn, trigger oxidative stress through inflammation, leading to diabetes-related complications. Additionally, hyperglycemia-related oxidative stress may cause macrophages to adopt an M1 polarization, leading to excessive production of inflammatory cytokines. Furthermore, hyperlipidemia, often linked to obesity-induced insulin resistance, contributes to chronic inflammation which further exacerbates periodontitis in diabetic patients[23].

The link between periodontitis and hypertension is driven mainly by systemic inflammation and immune system activation. The inflammation leads to endothelial dysfunction, a critical factor in the etiology of hypertension. Immune cells such as T cells, and cytokines, *e.g.*, interferon-gamma, which are involved in periodontitis and hypertension, damage blood vessels and increase sodium retention in the kidneys, thereby raising blood pressure. Additionally, chronic oral bacterial infections, particularly infections with *Porphyromonas gingivalis* which often occur in periodontitis, intensify systemic inflammation, thereby further contributing to hypertension and increasing the cardiovascular burden[24] (Figure 2).

Yang *et al*[25] published an intriguing paper, which was focused on the correlation between CP and CKD. Data from 22 studies on the clinical attachment level (CAL) and pocket probing depth (PPD) of CKD and non-CKD individuals were integrated. The results demonstrated that patients with CP were 1.54 times more likely to develop CKD than non-CP subjects (relative risk, RR: 1.54, 95%CI: 1.40-1.70). The incidence of CP in CKD patients was 1.98 times higher than that in healthy individuals (OR: 1.98, 95%CI: 1.53-2.57). Patients with CKD presented higher levels of CAL [standardized mean difference (SMD): 0.65, 95%CI: 0.29-1.01] and PPD (SMD: 0.33, 95%CI: 0.02-0.63), when compared to healthy controls. The study established a bidirectional association between CP and CKD through a meta-analysis of observational studies. Additionally, the risk of CKD was higher in patients with CP[25]. These findings are similar to those reported by Deschamps-Lenhardt *et al*[5]. In the latter study, a total of 37 articles from observational investigations were subjected to systematic review, out of which only 17 were used for the meta-analysis. The primary objective was to investigate the association between CP and CKD through analyses of related studies and studies on the effect of CP on renal health. The meta-analysis showed a positive association between CKD and PD, and the strength of the association increased when severe PD was considered [OR = 2.39 (1.70-3.36)]. This association was identified even after adjusting for major CKD risk factors or after using precise diagnostic criteria [OR = 2.26 for severe PD (1.69-3.01)][5]. In each of these studies[5,25], it was concluded that there was a strong correlation between CP and CKD. However, Yang *et al*[25] provided a more detailed analysis of how specific clinical parameters, *e.g.*, CAL and PPD are affected in patients with CKD, thereby highlighting the importance of oral health in managing systemic diseases. However, in contrast, Nanayakkara *et al*[26]

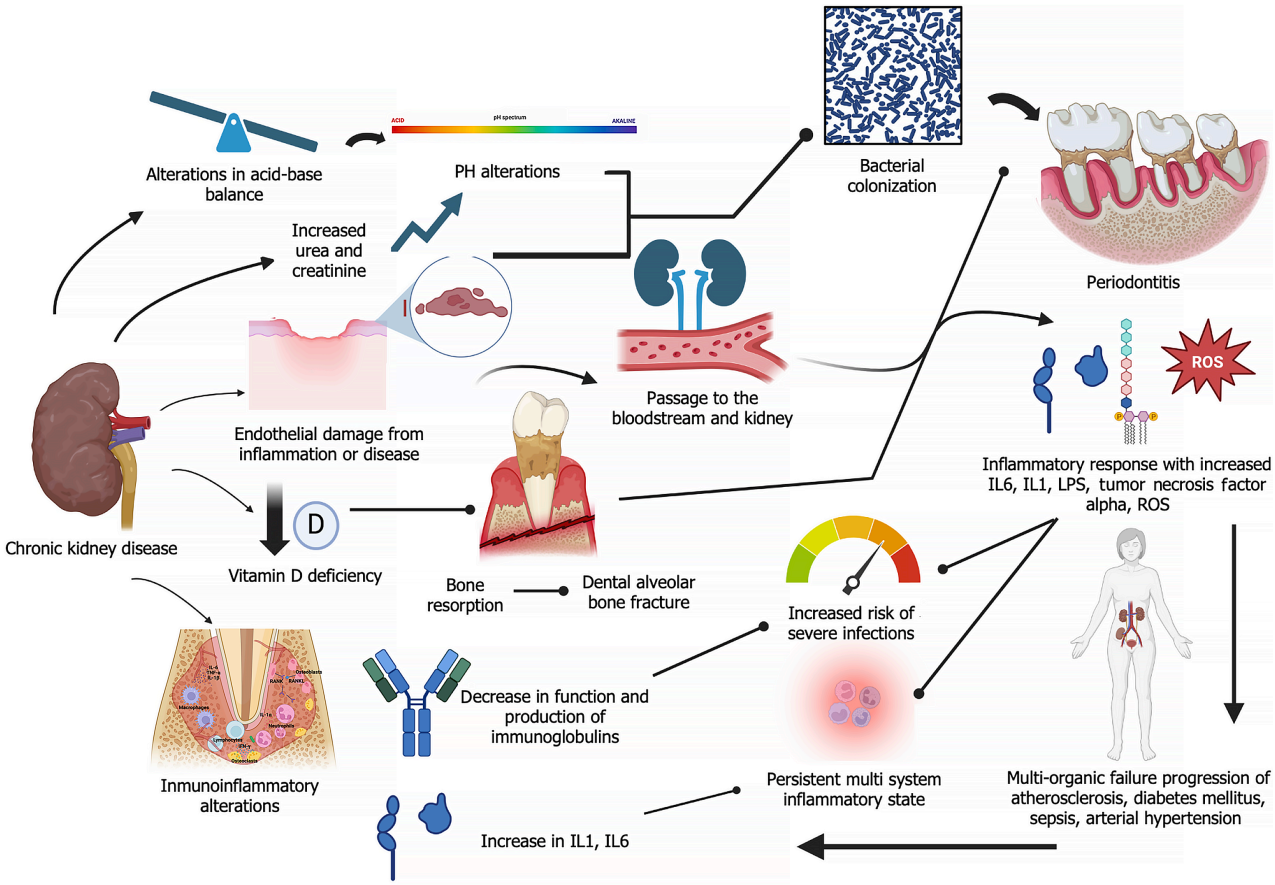

Figure 1 Image showing the main pathophysiological alterations in chronic kidney disease and periodontitis. The green arrows illustrate the alterations in periodontal disease and how the association of both conditions predisposes the patient to a persistent inflammatory state and multi-organ damage (Created with BioRender.com). IL1: Interleukin-1; IL6: Interleukin-6; LPS: lipopolysaccharide; ROS: Reactive oxygen species.

analyzed the possible association between CP and CKD through a systematic review and meta-analysis of observational studies reported in 47 articles. They concluded that participants with CP were 3.54 times more likely to have CKD than subjects without periodontitis, although significant heterogeneity was observed amongst the studies (I^2 = 88.3%, P < 0.001). However, the findings were inconclusive on directional association: The random effects model showed an incidence rate ratio (IRR) of 2.10, while the fixed effects model resulted in an IRR of 1.76, with significant heterogeneity (I^2 = 78.3%, P = 0.031)[26]. Therefore, the results indicated that there was a non-directional association between CP and CKD, although evidence for a causal association was limited. Thus, there is need for adequately designed prospective studies and longer follow-up periods in order to establish the causal relationship more clearly.

Although comparative studies provide valuable insights into the association between CP and CKD, it is essential to consider methodological limitations and potential biases in order to accurately interpret the results. The heterogeneities in the measurement methods, definitions and diagnostic criteria for CKD and CP, as well as the variabilities in the study populations presented in the study by Yang *et al*[25], may affect the validity of the findings. The research by Deschamps-Lenhardt *et al*[5] highlighted variabilities in the inclusion and exclusion criteria used in the integrated studies, which may compromise the representativeness of the results. Additionally, the absence of uniform adjustments for critical risk factors such as diabetes, smoking, and hypertension, may have introduced bias in the results, since these factors are associated with both CP and CKD. Furthermore, Nanayakkara *et al*[26] reported high heterogeneity (I^2 = 88.3%) amongst the integrated studies, indicating significant variabilities in study design, population, and outcome measures. These variabilities made it difficult for the researchers to conclusively establish the association between CP and CKD. Future studies should consider standardizing methods and definitions, rigorous adjustments for confounding factors, and employment of more robust designs, so as to enhance the quality and reliability of the findings.

CLINICAL IMPLICATIONS

Given the bidirectional relationship between CP and CKD, it is crucial for periodontists and nephrologists to collaborate closely in developing and implementing treatment strategies aimed at improving the management and outcomes of patients affected by the two concurrent diseases. Systemic inflammation and oxidative stress are underlying mechanisms that link both diseases. Thus, it is very likely that comprehensive management will significantly benefit patients' overall health.

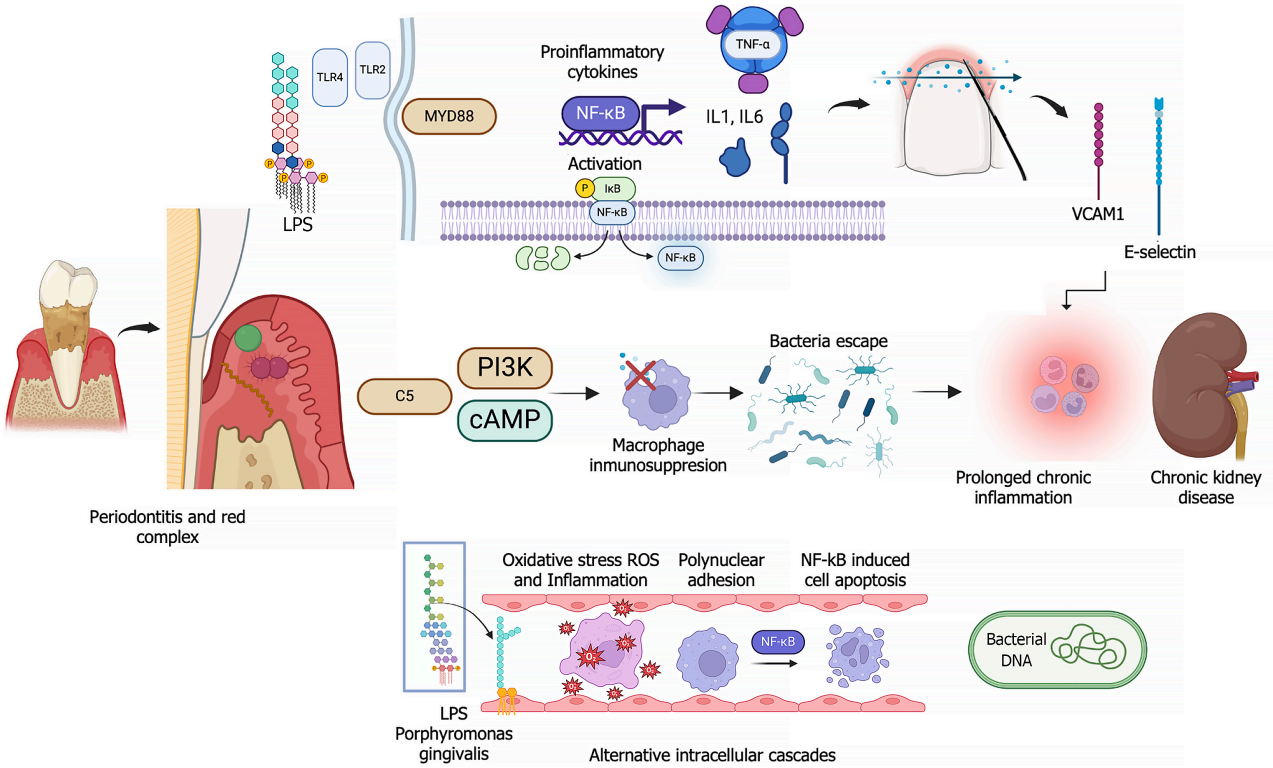

Figure 2 Bacteria from the "red complex" of periodontal disease, such as *Porphyromonas gingivalis*, activate toll-like receptors-2 and toll-like receptors-4 on immune cells *via* lipopolysaccharide. This activation triggers an inflammatory cascade mediated by MyD88 and nuclear transcription factor-kappa B (NF-kB), leading to the production of cytokines [interleukin (IL)-1, IL-6 and tumour necrosis factor alpha (TNF-α)] and adhesion molecules (VCAM1 and E-selectins). Intracellular pathways such as PI3K and cAMP induced by complement factor C5 suppress macrophage immune responses, thereby allowing pathogen survival and causing persistent inflammation. Oxidative stress driven by the presence of lipopolysaccharide from *P. gingivalis* and the production of reactive oxygen species leads to inflammation, polymorphonuclear adhesion and cellular apoptosis induced by NF-kB, which directly target bacterial DNA. This cycle of inflammation and oxidative stress exacerbates periodontal disease and chronic kidney disease, thereby negatively impacting renal and periodontal health (Created with BioRender.com). LPS: Lipopolysaccharide; TLR2: Toll-like receptors-2; TLR4: Toll-like receptors-4; MyD88: Myeloid differentiation primary response 88; NF-kB: Nuclear transcription factor-kappa B; TNF-α: Tumor necrosis factor alpha; IL1: Interleukin-1; IL6: Interleukin-6; IkB: Inhibitory protein; VCAM1: Vascular cell adhesion molecule 1; C5: Complement component 5; PI3K: Phosphoinositide 3-kinase; cAMP: Cyclic adenosine monophosphate; ROS: Reactive oxygen species.

It is essential for periodontists and nephrologists to work together to design, develop, and implement comprehensive treatment plans that address both periodontal and renal health. Effective communication and teamwork between these professionals are vital for early detection and timely intervention. In dental and nephrology clinics, it would be highly beneficial to design early detection programs for identifying patients at risk of developing CP and CKD. Early detection allows for preventive interventions that may slow down the progression of these conditions, while periodic evaluations of periodontal and renal health enable the early identification of changes and relevant treatment adjustments.

Specific periodontal therapeutic interventions and systemic inflammation control should be successfully implemented. Non-surgical and surgical periodontal therapies should be tailored in order to control the inflammatory process and reduce the bacterial load in CKD patients. Treatments should be personalized to meet each patient's specific needs. Regarding systemic inflammation control, interventions aimed at managing inflammation and oxidative stress such as the use of anti-inflammatory and antioxidant drugs, should be considered in order to improve both periodontal and renal health. It is crucial for healthcare professionals to be trained to recognize the signs and symptoms of CP and CKD, and it is vital to understand the importance of simultaneous management for the two conditions. Continuing education may enhance knowledge and cooperation among specialists.

In clinical practice, integrating these recommendations will significantly improve the management of patients with CP and CKD, thereby enhancing their quality of life and reducing the progression of the conditions. A multidisciplinary and comprehensive approach is essential for effectively addressing this bidirectional relationship and its implications for overall health.

FUTURE PERSPECTIVES

The findings presented in the meta-analysis by Yang *et al*[25] on the association between CP and CKD open several important directions for future research for enhancement of the understanding of this relationship.

Although the current study has established an association between CP and CKD, future research must ensure uniformity in the definition and classification of CP in order to guarantee more accurate comparisons and dose-response

analyses. It would be valuable to conduct randomized controlled trials to assess whether immune suppression induced by CKD increases susceptibility to CP. Additionally, it would be beneficial to investigate whether the systemic inflammatory response caused by CP leads to chronic pathological changes in renal function. Furthermore, more rigorous and consistent adjustment for confounding factors is required to reduce bias and obtain more reliable results. Research on the bidirectional relationship between CP and CKD would provide insights into how each condition may influence the other, and help develop comprehensive, multidisciplinary treatment strategies.

There is need for studies on the efficacy of specific periodontal health intervention such as non-surgical periodontal therapy, in improving renal outcomes. Randomized clinical trials aimed at investigating how periodontal treatment may influence CKD progression would be particularly valuable. Additionally, well-designed longitudinal cohort studies would be beneficial in assessing the long-term impact of periodontal interventions on renal health.

In summary, prioritizing these future research directions will not only deepen the understanding of the association between CP and CKD but also unravel the underlying mechanisms and yield more robust and precise conclusions on their relationship.

CONCLUSION

Although several studies have established an association between CP and CKD, the causal relationship between these two conditions remains uncertain due to the presence of multiple uncontrolled confounding factors in the analyzed studies. Additionally, the significant heterogeneity amongst studies suggests that the evidence is not yet conclusive enough to allow for proposal of a definitive association. Therefore, prospective research with adequate control and design are needed for the identification of the specific impact of CP on the progression of CKD, as well as studies on the specific interventions in periodontal health, in order to determine their direct effect on renal function. Until then, managing periodontal health in patients with CKD should be considered a general preventive measure without attributing a decisive influence on the progression of chronic kidney disease. Fostering interdisciplinary collaboration between periodontists and nephrologists is essential for the design, development, and implementation of treatment plans that address both periodontal and renal health. Public health policies should also prioritize the early detection and preventive management of CP and CKD by developing comprehensive health programs that integrate oral and renal care. These programs should ensure that all patients have access to quality care and promote preventive interventions to reduce the progression of both conditions. Additionally, awareness campaigns should be designed to educate the public on the importance of maintaining good oral health to prevent renal complications.

FOOTNOTES

Author contributions: Martínez Nieto M, Lomelí Martínez SM, De León Rodríguez ML and Anaya Macías RC contributed equally to the preparation of this manuscript; Lomelí Martínez SM and Martínez Nieto M conceptualized the study; Lomelí Martínez SM, Martínez Nieto M, De León Rodríguez ML and Anaya Macías RC performed literature searches; Lomelí Martínez SM, Martínez Nieto M, De León Rodríguez ML wrote the preliminary draft; Martínez Nieto M, Lomelí Martínez SM, De León Rodríguez ML and Anaya Macías RC critically reviewed and approved the manuscript.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest to disclose.

Country of origin: Mexico

ORCID number: Melissa Martínez Nieto 0009-0007-1843-384X; Martha Leticia De Leon Rodríguez 0009-0008-1068-4465; Rocio del Carmen Anaya Macias 0009-0007-8947-2109; Sarah Monserrat Lomelí Martínez 0000-0002-0569-1387.

S-Editor: Liu JH
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group**. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024; **105**: S117-S314 [PMID: 38490803 DOI: 10.1016/j.kint.2023.10.018]

2 **Sundström J**, Bodegard J, Bollmann A, Vervloet MG, Mark PB, Karasik A, Taveira-Gomes T, Botana M, Birkeland KI, Thuresson M, Jäger L, Sood MM, VanPottelbergh G, Tangri N; CaReMe CKD Investigators. Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2·4 million patients from 11 countries: The CaReMe CKD study. *Lancet Reg Health Eur* 2022; **20**: 100438

[PMID: 36090671 DOI: 10.1016/j.lanepe.2022.100438]

3 **Chaudhry A**, Kassim NK, Zainuddin SLA, Taib H, Ibrahim HA, Ahmad B, Hanafi MH, Adnan AS. Potential Effects of Non-Surgical Periodontal Therapy on Periodontal Parameters, Inflammatory Markers, and Kidney Function Indicators in Chronic Kidney Disease Patients with Chronic Periodontitis. *Biomedicines* 2022; **10** [PMID: 36359271 DOI: 10.3390/biomedicines10112752]

4 **Wu H**, Wang S, Wei Z. Periodontitis and risk of mortality in patients with chronic kidney disease: A systematic review with meta-analysis. *J Periodontal Res* 2024; **59**: 868-876 [PMID: 38501242 DOI: 10.1111/jre.13255]

5 **Deschamps-Lenhardt S**, Martin-Cabezas R, Hannedouche T, Huck O. Association between periodontitis and chronic kidney disease: Systematic review and meta-analysis. *Oral Dis* 2019; **25**: 385-402 [PMID: 29377446 DOI: 10.1111/odi.12834]

6 **Mahendra J**, Palathingal P, Mahendra L, Alzahrani KJ, Banjer HJ, Alsharif KF, Halawani IF, Muralidharan J, Annamalai PT, Verma SS, Sharma V, Varadarajan S, Bhandi S, Patil S. Impact of Red Complex Bacteria and TNF-α Levels on the Diabetic and Renal Status of Chronic Kidney Disease Patients in the Presence and Absence of Periodontitis. *Biology (Basel)* 2022; **11** [PMID: 35336824 DOI: 10.3390/biology11030451]

7 **Schütz JDS**, de Azambuja CB, Cunha GR, Cavagni J, Rösing CK, Haas AN, Thomé FS, Fiorini T. Association between severe periodontitis and chronic kidney disease severity in predialytic patients: A cross-sectional study. *Oral Dis* 2020; **26**: 447-456 [PMID: 31742816 DOI: 10.1111/odi.13236]

8 **Kapellas K**, Singh A, Bertotti M, Nascimento GG, Jamieson LM; Perio-CKD collaboration. Periodontal and chronic kidney disease association: A systematic review and meta-analysis. *Nephrology (Carlton)* 2019; **24**: 202-212 [PMID: 29359889 DOI: 10.1111/nep.13225]

9 **Chang JF**, Yeh JC, Chiu YL, Liou JC, Hsiung JR, Tung TH. Periodontal Pocket Depth, Hyperglycemia, and Progression of Chronic Kidney Disease: A Population-Based Longitudinal Study. *Am J Med* 2017; **130**: 61-69.e1 [PMID: 27615146 DOI: 10.1016/j.amjmed.2016.08.024]

10 **Hickey NA**, Shalamanova L, Whitehead KA, Dempsey-Hibbert N, van der Gast C, Taylor RL. Exploring the putative interactions between chronic kidney disease and chronic periodontitis. *Crit Rev Microbiol* 2020; **46**: 61-77 [PMID: 32046541 DOI: 10.1080/1040841X.2020.1724872]

11 **Chatzopoulos GS**, Jiang Z, Marka N, Wolff LF. Periodontal Disease, Tooth Loss, and Systemic Conditions: An Exploratory Study. *Int Dent J* 2024; **74**: 207-215 [PMID: 37833208 DOI: 10.1016/j.identj.2023.08.002]

12 **Hajishengallis G**. Interconnection of periodontal disease and comorbidities: Evidence, mechanisms, and implications. *Periodontol 2000* 2022; **89**: 9-18 [PMID: 35244969 DOI: 10.1111/prd.12430]

13 **Gamonal J**, Bravo J, Malheiros Z, Stewart B, Morales A, Cavalla F, Gomez M. Periodontal disease and its impact on general health in Latin America. Section I: Introduction part I. *Braz Oral Res* 2020; **34**: e024 [PMID: 32294677 DOI: 10.1590/1807-3107bor-2020.vol34.0024]

14 **Fischer RG**, Lira Junior R, Retamal-Valdes B, Figueiredo LC, Malheiros Z, Stewart B, Feres M. Periodontal disease and its impact on general health in Latin America. Section V: Treatment of periodontitis. *Braz Oral Res* 2020; **34**: e026 [PMID: 32294679 DOI: 10.1590/1807-3107bor-2020.vol34.0026]

15 **Li L**, Zhang YL, Liu XY, Meng X, Zhao RQ, Ou LL, Li BZ, Xing T. Periodontitis Exacerbates and Promotes the Progression of Chronic Kidney Disease Through Oral Flora, Cytokines, and Oxidative Stress. *Front Microbiol* 2021; **12**: 656372 [PMID: 34211440 DOI: 10.3389/fmicb.2021.656372]

16 **Loos BG**, Van Dyke TE. The role of inflammation and genetics in periodontal disease. *Periodontol 2000* 2020; **83**: 26-39 [PMID: 32385877 DOI: 10.1111/prd.12297]

17 **Hajishengallis G**, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. *Nat Rev Immunol* 2021; **21**: 426-440 [PMID: 33510490 DOI: 10.1038/s41577-020-00488-6]

18 **Tai YH**, Chen JT, Kuo HC, Chang WJ, Wu MY, Dai YX, Liu WC, Chen TJ, Wu HL, Cherng YG. Periodontal disease and risk of mortality and kidney function decline in advanced chronic kidney disease: a nationwide population-based cohort study. *Clin Oral Investig* 2021; **25**: 6259-6268 [PMID: 33813639 DOI: 10.1007/s00784-021-03924-6]

19 **Vachhani KS**, Bhavsar NV. Effects of non-surgical periodontal therapy on serum inflammatory factor high-sensitive C-reactive protein, periodontal parameters and renal biomarkers in patients with chronic periodontitis and chronic kidney disease. *Dent Med Probl* 2021; **58**: 489-498 [PMID: 34816635 DOI: 10.17219/dmp/136034]

20 **Lertpimonchai A**, Rattanasiri S, Tamsailom S, Champaiboon C, Ingsathit A, Kitiyakara C, Limpianunchai A, Attia J, Sritara P, Thakkinstian A. Periodontitis as the risk factor of chronic kidney disease: Mediation analysis. *J Clin Periodontol* 2019; **46**: 631-639 [PMID: 30993705 DOI: 10.1111/jcpe.13114]

21 **Palathingal P**, Mahendra J, Annamalai PT, Varma SS, Mahendra L, Thomas L, Baby D, Jose A, Srinivasan S, R A. A Cross-Sectional Study of Serum Glutathione Peroxidase: An Antioxidative Marker in Chronic Periodontitis and Chronic Kidney Disease. *Cureus* 2022; **14**: e22016 [PMID: 35340502 DOI: 10.7759/cureus.22016]

22 **Kanzaki H**, Wada S, Narimiya T, Yamaguchi Y, Katsumata Y, Itohiya K, Fukaya S, Miyamoto Y, Nakamura Y. Pathways that Regulate ROS Scavenging Enzymes, and Their Role in Defense Against Tissue Destruction in Periodontitis. *Front Physiol* 2017; **8**: 351 [PMID: 28611683 DOI: 10.3389/fphys.2017.00351]

23 **Shinjo T**, Nishimura F. The bidirectional association between diabetes and periodontitis, from basic to clinical. *Jpn Dent Sci Rev* 2024; **60**: 15-21 [PMID: 38098853 DOI: 10.1016/j.jdsr.2023.12.002]

24 **Szczepaniak P**, Mikołajczyk TP, Cześnikiewicz-Guzik M, Guzik TJ. Periodontitis as an inflammatory trigger in hypertension: From basic immunology to clinical implications. *Kardiol Pol* 2021; **79**: 1206-1214 [PMID: 34847238 DOI: 10.33963/KP.a2021.0161]

25 **Yang F**, Shu CJ, Wang CJ, Chen K. Meta-analysis of the association between chronic periodontitis and chronic kidney disease. *World J Clin Cases* 2024; **12**: 5094-5107 [PMID: 39109009 DOI: 10.12998/wjcc.v12.i22.5094]

26 **Nanayakkara S**, Zhou X. Periodontitis May Be Associated With Chronic Kidney Disease, but Evidence on Causal Association Is Limited. *J Evid Based Dent Pract* 2019; **19**: 192-194 [PMID: 31326054 DOI: 10.1016/j.jebdp.2019.05.014]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6782-6790

DOI: 10.12998/wjcc.v12.i35.6782

ISSN 2307-8960 (online)

EDITORIAL

Cytokine release syndrome induced by anti-programmed death-1 treatment in a psoriasis patient: A dark side of immune checkpoint inhibitors

José Luis Maldonado-García, Ana Fragozo, Lenin Pavón

Specialty type: Immunology

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 B

P-Reviewer: Yu S

Received: July 31, 2024
Revised: August 26, 2024
Accepted: September 9, 2024
Published online: December 16, 2024
Processing time: 85 Days and 8.8 Hours

José Luis Maldonado-García, Departamento de Bioquímica, Facultad de Medicina, Universidad Nacional Autónoma de México, Coyoacán 04510, Ciudad de México, Mexico

José Luis Maldonado-García, Departamento de Inmunología, Escuela Nacional de Ciencias Biológicas, Mexico City 1134, Ciudad de México, Mexico

Ana Fragozo, Unidad de Desarrollo e Investigación en Bioterapéuticos, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City 11340, Ciudad de México, Mexico

Lenin Pavón, Laboratorio de Psicoinmunología, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Mexico City 11340, Mexico

Corresponding author: Lenin Pavón, PhD, Professor, Laboratorio de Psicoinmunología, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, 101 Calzada México-Xochimilco, Mexico City 11340, Mexico. lkuriaki@inprf.gob.mx

Abstract

In recent years, cancer immunotherapy has introduced novel treatments, such as monoclonal antibodies, which have facilitated targeted therapies against tumor cells. Programmed death-1 (PD-1) is an immune checkpoint expressed in T cells that regulates the immune system's activity to prevent over-activation and tissue damage caused by inflammation. However, PD-1 is also expressed in tumor cells and functions as an immune evasion mechanism, making it a therapeutic target to enhance the immune response and eliminate tumor cells. Consequently, immune checkpoint inhibitors (ICIs) have emerged as an option for certain tumor types. Nevertheless, blocking immune checkpoints can lead to immune-related adverse events (irAEs), such as psoriasis and cytokine release syndrome (CRS), as exemplified in the clinical case presented by Zhou *et al* involving a patient with advanced gastric cancer who received sintilimab, a monoclonal antibody targeting PD-1. Subsequently, the patient experienced exacerbation of psoriasis and CRS. The objective of this editorial article is to elucidate potential immunologic mechanisms that may contribute to the development of CRS and psoriasis in patients receiving ICIs. It is crucial to acknowledge that while ICIs offer superior safety and efficacy compared to conventional therapies, they can also manifest irAEs affecting the skin, gastrointestinal tract, or respiratory system. In severe cases, these irAEs can

lead to life-threatening complications such as circulatory shock or multiorgan failure. Consequently, it is recommended that patients receiving ICIs undergo regular monitoring to identify and manage these adverse events effectively.

Key Words: Immune checkpoints inhibitors; Programmed death-1; Cancer immunotherapy; Psoriasis; Cytokine release syndrome; Immune-related adverse events

Core Tip: The introduction of cancer immunotherapies, particularly the utilization of monoclonal antibodies that inhibit immune checkpoints, has yielded significant benefits, including enhanced survival rates and a diminished likelihood of adverse effects. However, immune-related adverse events can manifest in certain patients, presenting mild symptoms such as fever, fatigue, headache, rash, arthralgia, and myalgia. In more severe cases, circulatory shock or multiorgan failure can occur, which can be mortal. This editorial examines the possible immunologic mechanisms underlying cytokine release syndrome and the exacerbation of psoriasis in patients receiving anti-programmed death-1 monoclonal antibodies.

Citation: Maldonado-García JL, Fragozo A, Pavón L. Cytokine release syndrome induced by anti-programmed death-1 treatment in a psoriasis patient: A dark side of immune checkpoint inhibitors. *World J Clin Cases* 2024; 12(35): 6782-6790
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6782.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6782

INTRODUCTION

Currently, there is revolutionary progress in cancer therapies, introducing new treatments to eliminate tumor cells, as the "magic bullets" proposed by Paul Ehrlich in the 20th century[1,2]. These treatments are based on biotechnological advances that made it possible to generate immunotherapies using highly-specific monoclonal antibodies or adoptive cell therapy treatments to prolong survival and significantly improving the quality of life of patients[3,4].

Cancer immunotherapy has many advantages such as greater precision and efficacy in eliminating tumor cells, restoration of immune system that contributes to tumor cells killing, and a higher long-term survival rate and lower incidence of adverse effects than conventional treatments[5]. Despite the potential of cancer immunotherapy, we must consider important aspects. Not all patients are suitable candidates for these treatments, and the high costs involved are a significant concern. Furthermore, immunotherapy may lead to immune-mediated complications and unspecific responses and even trigger autoimmune diseases or systemic inflammation, potentially resulting in patient fatalities[5,6].

The case reported by Zhou *et al*[7] about a patient with advanced gastric cancer who received sintilimab, a monoclonal antibody against programmed death 1 (PD-1), a membrane protein expressed on T lymphocytes, is an example of an immune-mediated complication is t. The patient developed severe rashes accompanied by cytokine release syndrome (CRS). In addition, the patient had a medical history of infantile paralysis, hypertension, diabetes mellitus, and plaque psoriasis. As antitumor therapy, the patient received a regimen of oxaliplatin, capecitabine, and sintilimab. Despite this, the patient developed an exacerbated low-grade skin rash accompanied by fever, with a body temperature of 38 °C. Finally, CRS and psoriasis were diagnosed. This editorial article discusses the immunological mechanisms behind the exacerbation of psoriasis secondary to administration of immune checkpoint inhibitors (ICIs) such as sintilimab. Although immune-mediated side effects to the use of ICI are rare, first-contact physicians and non-oncology specialists who provide clinical follow-up to patients must consider them to provide early interventions upon suspicion of these complications.

IMMUNE CHECKPOINT INHIBITORS AND CYTOKINE RELEASE SYNDROME

The substantial advances in cancer therapies have prolonged patients' survival and significantly improved their life quality. Novel cancer immunotherapies include adoptive cell therapy (ACT) and ICI[3,4]. ACT involves the transfer of modified or unmodified T cells to eradicate cancer cells. T cell modification is initially performed by extracting T cells from the patient, followed by genetic modification to express specific receptors on their surface[8]. Receptors that can be modified include chimeric antigen receptors (CAR), designed to recognize and bind to specific proteins on the surface of cancer cells. CAR-T receptors contain an antigen recognition domain and an intracellular signaling domain able to activate efficiently and co-stimulate lymphocytes and T cell receptors to recognize specific antigens presented by cancer cells *via* major histocompatibility complex (MHC)[9]. Meanwhile, ACT without receptor modification consists only of extracting T cells, performing an *ex-vivo* expansion, and finally infusing the expanded T cells back into the patient to eliminate cancer cells[10].

The mechanism of action of ICIs is based on stimulating the T-cell-mediated response to destroy tumor cells. These treatments stimulate immune responses to cancer cells by blocking immune checkpoints[8]. Immune checkpoints function as an on/off switch of the immune system and maintain the homeostatic balance between suppression and activation to prevent an overactivation of the immune system[11]. As examples of immune checkpoints, we could mention PD-1, programmed death-ligand 1 (PD-L1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), B7 homolog 3 protein, B7 homolog 4 protein, leukocyte immunoglobulin-like receptor B1, leukocyte immunoglobulin-like receptor B2, lymphocyte activation gene 3, T-cell immunoglobulin and mucin containing protein-3, CD47, CD137, and CD70[11,12]. Immune checkpoint markers are highly expressed in cancer cells and are critical in tumor cells' immune evasion mechanisms. Furthermore, immune checkpoints favor the maintenance of tumor cell malignancy, promoting self-renewal, epithelial-mesenchymal transition, metastasis, drug resistance, anti-apoptosis, angiogenesis, or improvement of energy metabolism [12,13]. Currently, available ICIs are monoclonal antibodies directed against CTLA-4, PD-1, or PD-L1. CTLA-4 acts as an initial brake on T-cell activation, while PD-1 and PD-L1 prevent excessive T-cell activation and chronic inflammation. ICIs favor increased T-cell activation after blocking PD-1 or CTLA-4 pathways, causing a more effective antitumor response [14-16].

CYTOKINE RELEASE SYNDROME AS A COMPLICATION ARISING FROM THE USE OF IMMUNE CHECKPOINT INHIBITORS

Overactivation of T cells by ICIs can trigger a series of toxic effects known as immune-related adverse events (irAEs)[17]. This can occur in any organ, although they commonly affect barrier organs (*i.e.*, the skin, gastrointestinal tract, lungs, and the liver) due to their direct exposure, and role in metabolism and elimination, as well as the inherent sensitivity to the harmful effects of treatments[17-19]. In this way, patients with autoimmune diseases, such as rheumatoid arthritis or Crohn's disease, have a higher risk of developing some irAEs secondary to the use of ICI due to the inflammatory environment that favors the appearance of adverse events[20,21]. Patients with psoriasis also exhibit an increased risk of developing irAE when undergoing ICI treatments[22]. Another immune-related adverse effect due to ICI use is CRS, although only a few cases have been reported[6,23,24].

The incidence of IrAEs in patients receiving ICIs varies depending on the treatment regimen[25]. For instance, administering anti-CTLA-4 antibodies (ipilimumab) is linked to a 60% risk of developing IrAEs of any severity, with only 10%-30% of cases resulting in severe manifestations[26]. Notably, the occurrence and severity of immune-mediated adverse effects secondary to using anti-CTLA-4 antibodies show a dose-dependent pattern[26,27]. In contrast, the use of anti-PD-1 antibodies is associated with a lower risk of developing IrAEs, with an estimated incidence of approximately 10% among patients. Of these, 5%-20% may experience severe IrAEs[25,28]. The combination of immune checkpoint inhibitors, such as the combination of an anti-CTLA-4 antibody with an anti-PD-1 antibody, increases the severity and incidence of IrAEs by approximately 30%. Moreover, these adverse effects appear at earlier stages of combined treatment compared to monotherapy[25,29].

Cytokine release syndrome (CRS), defined as a systemic inflammatory response due to the release of inflammatory mediators such as cytokines, chemokines, oxygen radicals, complement factors, and coagulation[30,31], was described in the early 1990s when the murine monoclonal antibody directed against the human T-cell receptor CD3 complex, also called Muromonab-CD3 or OKT3, was introduced as an immunosuppressive treatment during solid organ transplantation. Initially, the term "cytokine release syndrome" was used in the context of cancer immunotherapy now[32]. CRS is described in other clinical settings such as viral infections caused by influenza or SARS-CoV-2[33,34]; in hematopoietic cell transplantation and graft-versus-host disease[35,36]; and as previously mentioned, in cancer immunotherapies such as ICI[24,37], bispecific T cell engagers (BiTes)[31,38] and CAR–T cells[31,39].

Although the pathophysiology of CRS is not fully understood, the activation of several cell populations, including activated myeloid cells like monocytes/macrophages, dendritic cells, and/or activated lymphocytes such as natural killer cells, T cells, and B cells; and/or non-immune cells, *i.e.*, endothelial cells has been suggested as the main proposal. Moreover, there is a characteristic increase in serum tumor necrosis factor alpha (TNF-α) and interferon-γ during the first 1-2 hours, followed by increases in circulating interleukin (IL)-6 and IL-10, and in some cases, IL-2 and IL-8[30,32,40]. CRS has a broad spectrum of symptoms, varying from mild symptoms, including fever, fatigue, headache, rash, arthralgia, and myalgia[41,42]. Severe CRS cases are characterized by hypotension and high fever. They may progress to a systemic inflammatory response complicated by circulatory shock, vascular leakage, disseminated intravascular coagulation, and multiorgan failure[30].

PSORIASIS INDUCED BY ANTI-PD-1 THERAPY

Psoriasis is a chronic inflammatory disease primarily affecting the skin and joints, characterized by erythema, thickening, and skin scaling[43]. Psoriasis is caused by a complex interplay between genetic factors, external and internal triggers, and immunological factors[44]. The genetic factors of psoriasis involve nine genomic regions (PSORS 1-9) where HLA-C*06: 02 (PSORS 1) is the allele most closely related to disease susceptibility and severity[45]. Immunologically, psoriasis pathophysiology involves a complex interplay between innate and adaptive immune response mechanisms. It has been proposed that psoriasis has a mixed pattern of autoimmune and autoinflammatory disease[46,47], both of which will be discussed below.

External or internal factors can trigger psoriasis. External factors include infections by bacteria such as *Staphylococcus aureus* and *Streptococcus pyogenes*, viruses including human papillomavirus or retroviruses, fungi like *Malassezia* and *Candida albicans*[48]; skin injuries (cuts and burns)[49]; obesity, smoking or excessive alcohol consumption[50,51]. On the other hand, internal factors include dysbiosis in the skin and gut microbiome[48,52], stress[51], dyslipidemia[53] and, in women, a dysregulation of progesterone and estrogen can exacerbate symptoms[54-56].

External triggers such as skin trauma, dysbiosis, or smoking cause keratinocytes to release antimicrobial peptides such as cathelicidin (LL37)[57], S100 family proteins like S100A7 (psoriacin), S100A8 (calgranulin A), and S100A9 (Calgranulin B)[58] and β-defensins[59]. These antimicrobial peptides bind to the DNA or RNA of damaged cells[60], forming complexes, such as the DNA-LL37, which activates plasmacytoid dendritic cells (pDC) through toll-like receptors (TLR) 7, which triggers the production of type I interferons (IFN), like IFN-α and -β complex[61]. In addition, the RNA-LL37 complex activates myeloid dendritic cells through TLR8, promoting the release of TNF-α, IL-23, and IL-12[60,62]. After recognizing the DNA-LL-37 complex, mature DCs upregulate CCR7 expression and migrate to draining lymph nodes through a process finely regulated by chemokines and their receptors. In lymph nodes, DCs present antigens to naive T cells through the MHC, providing co-stimulatory signals and activating T cell proliferation and differentiation. Simultaneously, IL-23 secreted by activated DCs favors the differentiation of T helper 17 (Th17) cells, known to produce IL-17A/F, IL-22, and TNF-α. Furthermore, IL-12 secreted by DCs induces the differentiation of T helper 1 (Th1) cells, which produce IFN-γ, IL-2, and TNF-α[63-65]. The autoreactive T cells migrate to the epidermis, where they will continue to produce Th1 and Th17 cytokines, which cause the proliferation and activation of keratinocytes, forming the characteristic thickening of the epidermis and the appearance of psoriatic plaques[66].

As previously mentioned, psoriasis includes features of an autoimmune disease, such as antigen presentation *via* MHC and activation of Th1 and Th17 lymphocytes that favor the activation of phagocytes, such as macrophages or neutrophils. Likewise, psoriasis has features of autoinflammatory disease, such as persistent activation of alarmins and damage signals that activate TLRs, chemotaxis, and activation of monocytes. It is important to emphasize that the activity of Th1 and Th17 lymphocytes feedback to the function of innate cells such as macrophages and neutrophils and vice versa[46,47,67].

In addition to the etiopathogenic mechanisms previously described for psoriasis, other factors that might contribute to the development of the disease include the use of certain drugs such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, lithium, anti-malaria drugs, interferons, terbinafine, bupropion, immunosuppressants, and antineoplastics such as nivolumab (monoclonal antibody anti-PD-1) and imatinib[68,69].

Some patients with anti-TNF-α therapy (infliximab, etanercept, adalimumab, and certolizumab) displayed a subtype of psoriasis named paradoxical psoriasis[70,71]. However, the pathophysiology of drug-induced psoriasis remains unclear. Nonetheless, the disease has clinical differences depending on the drug that triggers it. For instance, an increase of IFN-α and pDC in lesions has been observed in paradoxical psoriasis caused by anti-TNF-α therapies; other findings include eczematiform spongiotic pattern, psoriasis-like dermatitis (with infiltration of intraepidermal or subcorneal neutrophils); and lichenoid reaction with focal interface dermatitis[70,71]. In contrast, anti-PD-1-induced psoriasis has histopathological features that are similar to chronic psoriasis, in which a predominance of adaptive immunity is observed, with abundant CD3+, CD8+ T cells and CD11c+ dendritic cells infiltrating the skin lesions, as well as an increase in IL-23, IL-6, TNF-α, IFN-γ, and IL-17[72].

Inhibition of the PD-1 immunomodulatory pathway can result in hyperactivation of Th1 and Th17 lymphocytes[73]. In physiological situations, PD-1 activation inhibits T and B cell signaling pathways, reducing cytokine production and cell proliferation and promoting apoptosis. This mechanism contributes to regulating the immune response, preventing overactivation of the immune system[74]. A remarkable example of this effect is the case presented by Zhou *et al*[7], in which a patient with advanced gastric cancer and chronic plaque psoriasis developed a severe CRS after treatment with sintilimab, a PD-1 inhibitor.

PD-1-inhibitor-induced psoriasis is presumably caused by the activation of various cell populations such as neutrophils, dendritic cells, Th1 and Th7 cells, and Treg cells[75]. In addition, dendritic cells release cytokines such as IFN-γ, IL-1, IL-17, and IL-22, which are associated with the development of de novo psoriasis or exacerbation of psoriasis [61,64,65]. The use of anti-PD-1 monoclonal antibodies can increase the half-life of neutrophils, as well as the increase of Th1 and Th17 cells, leading to a rise in the production of proinflammatory cytokines such as IL-2, IL-6, IL-12, IL-17, IL-22, IFN-γ, among others[75]. Also, over-activation of effector T cells can trigger CRS due to increased IFN-γ, TNF-α, and IL-6 [30,76]. The evidence suggests that CRS and Th1/Th17 cell overactivation and IL-6 release are responsible for developing anti-PD-1 induced psoriasis (Figure 1)[75,77,78]. Data obtained from animal models of anti-PD-1-induced psoriasis indicate that IL-6 elevation in plasma plays a crucial role in developing skin lesions and promotes CD8 T-cell infiltration into the epidermis[77]. Furthermore, CD8+ T cells were observed to enhance IFN-γ production resulting in keratinocyte activation[77]. Macrophages also participate in the activation and proliferation of keratinocytes through the release of TNF-α, macrophage migration inhibitory factor, and IL-20, and facilitate the angiogenesis observed in psoriasis by releasing vascular endothelial growth factor, transforming growth factor-β, platelet-derived growth factor, and TNF-α[22,75].

Several studies have evaluated the baseline levels and changes in cytokines in patients with different types of cancer treated with ICI. In patients treated with anti-PD1, no significant differences were observed in TNF-α levels before and after treatment; on the contrary, elevated IL-6 Levels are associated with worse outcomes in terms of treatment response and an increased risk of irAE. However, an increase in IL-1β levels when using an anti-PD1 has been related to a better response, as has IFN-γ[79]. These studies suggest that increased levels of several cytokines, such as IL-1β, IL-6, IFN-γ, and TNF-α after ICI treatment are associated with an increased response rate or an increased predisposition to irAE, which would lead to discontinuation or suppression of Anti-PD1 treatment[79,80]. These results emphasize the importance of monitoring the levels of these cytokines during treatment to identify patients who might benefit from closer follow-up

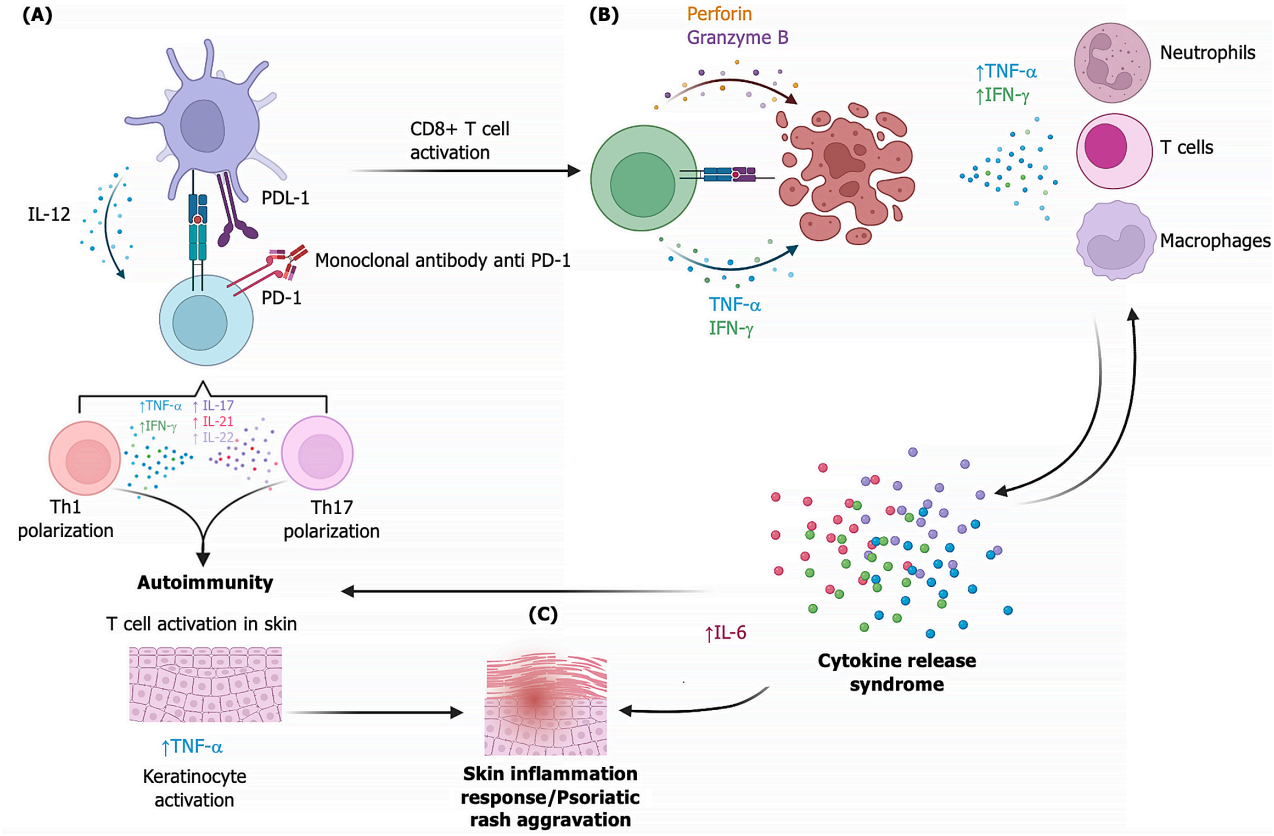

Figure 1 Possible immunologic mechanisms of anti programmed death-1 induced psoriasis. It has been proposed that programmed death-1 (PD-1) blockade enhances T cell activation, which results in two main events. A: Increased T helper 1/T helper 17 cell differentiation, which may induce autoimmunity; B: Blocking PD-1 increases CD8+ T cell activity and increased antitumor activity, which may trigger cytokine release syndrome, which increases the risk of developing autoimmunity; C: Blocking PD-1 increases CD8+ T cell activity and increased antitumor activity, which may trigger cytokine release syndrome, which increases the risk of developing autoimmunity. Finally, both pathways may induce a skin inflammatory response which promotes psoriatic skin lesions, possibly due to activation of keratinocytes by inflammatory mediators such as interleukin-6, interferon-γ and tumor necrosis factor-α. PDL-1: Programmed cell death ligand; PD-1: Programmed death-1; Th1: T helper 1; IL-6: interleukin-6; TNF-α: Tumor necrosis factor α; IFN-γ: Interferon-γ.

and make a timely therapeutic adjustment. In addition, these findings may help develop more effective strategies to prevent and treat adverse effects in the future.

According to previous reports, most cases of psoriasis induced by anti-PD-1 therapies present as exacerbations of psoriasis, and in some cases, de novo psoriasis lesions appear. The average time of symptom onset has been reported to be 10 weeks. In addition, no correlation has been reported between the severity of the antitumor response and psoriasis symptoms[72,73,75,81].

Anti-PD-1-induced psoriasis is classified into Grade I, Grade II, and Grade III according to the Common Criteria for Adverse Event Evaluation (CTCAE v5.0) classification, which considers the following parameters: Psoriasis area and severity index; body surface area; and investigator's global assessment[82]. Most of these patients develop grades I or II, with only a few reaching grade III. An algorithm has been proposed for the management of these patients. Initially, it is recommended to perform a directed interrogation for a history of psoriasis. If the patient has a history of psoriasis, it is recommended to monitor closely for irAE[73,82,83]. For the treatment of psoriasis, it is recommended that patients with grade 1 receive topical treatment, such as corticosteroids and vitamin D analogs, maintaining their current dose of ICI; patients with grade II should be treated with systemic therapies, such as phototherapy and retinoids, in addition to the measures of grade I treatment, with continuation or adjustment of the dose of ICI. Subsequently, the evolution should be evaluated two weeks later. Patients with Grade III psoriasis should be treated with higher doses of traditional systemic therapy based on grade II management. If treatment fails or the patient shows deterioration, the use of biological drugs such as TNF-α antagonists or IL-17A/IL-23 antagonists (Guselkumab or Secukinumab), can be considered, in addition to which the ICI regimen should be adjusted[83,84].

Although the incidence of anti-PD-1 induced psoriasis is relatively low, it is essential to consider that the use of ICI is not exempt from developing adverse events, in addition to the fact that the clinical follow-up given to these patients should be multidisciplinary to carry out effective interventions and minimize the damage caused by irAE in patients[22,73,81]

CONCLUSION

Cancer immunotherapy has made significant progress, and novel treatments have emerged to bolster the immune system's ability to eliminate tumor cells. Immune checkpoints, such as PD-1 or CTLA-4, are crucial in reducing the risk of excessive inflammation. Still, they are also expressed by tumor cells and facilitate evasion of the immune system. Consequently, they have been identified as therapeutic targets for cancer treatment. However, blocking immune checkpoints can lead to irAEs secondary to exacerbated inflammation, which may manifest as skin symptoms like psoriasis. The potential mechanisms underlying anti-PD-1-induced psoriasis, as described by Zhou *et al*[7] clinical case, involve an immune imbalance resulting from enhanced CD4+ and CD8+ T cell function due to PD-1 blockade. Increased CD4+ T cell activity promotes differentiation of Th1/Th17 cells, while improved CD8+ T cell activity favors antitumor activity that may trigger cytokine release syndrome. Both events contribute to keratinocyte activation through IL-6 and TNF-α, leading to the development of psoriasis lesions. Although these adverse events occur in a minority of patients, they serve as a clear reminder of the imperative for caution and meticulous attention to detail in the clinical evaluation of patients before the administration of immunotherapy with ICIs.

FOOTNOTES

Author contributions: Pavón L and Maldonado-García JL collaborated in designing the general concept and structure of the manuscript. Fragozo A, Maldonado-Garcia JL, and Pavón L wrote and edited the manuscript and reviewed the literature. Fragozo A and Maldonado-García JL designed the figure.

Supported by Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, No. NC23189.0.

Conflict-of-interest statement: All authors declare that there are no conflicts of interest.

Country of origin: Mexico

ORCID number: José Luis Maldonado-García 0000-0003-2694-1290; Ana Fragozo 0000-0001-5985-675x; Lenin Pavón 0000-0002-6067-6868.

S-Editor: Liu JH
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Zipfel PF**, Skerka C. From magic bullets to modern therapeutics: Paul Ehrlich, the German immunobiologist and physician coined the term 'complement'. *Mol Immunol* 2022; **150**: 90-98 [PMID: 36027818 DOI: 10.1016/j.molimm.2022.08.002]
2 **Strebhardt K**, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. *Nat Rev Cancer* 2008; **8**: 473-480 [PMID: 18469827 DOI: 10.1038/nrc2394]
3 **Papież MA**, Krzyściak W. Biological Therapies in the Treatment of Cancer-Update and New Directions. *Int J Mol Sci* 2021; **22** [PMID: 34769123 DOI: 10.3390/ijms222111694]
4 **Debela DT**, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, Kitui SK, Manyazewal T. New approaches and procedures for cancer treatment: Current perspectives. *SAGE Open Med* 2021; **9**: 20503121211034366 [PMID: 34408877 DOI: 10.1177/20503121211034366]
5 **Tan S**, Li D, Zhu X. Cancer immunotherapy: Pros, cons and beyond. *Biomed Pharmacother* 2020; **124**: 109821 [PMID: 31962285 DOI: 10.1016/j.biopha.2020.109821]
6 **Yin Q**, Wu L, Han L, Zheng X, Tong R, Li L, Bai L, Bian Y. Immune-related adverse events of immune checkpoint inhibitors: a review. *Front Immunol* 2023; **14**: 1167975 [PMID: 37304306 DOI: 10.3389/fimmu.2023.1167975]
7 **Zhou MH**, Ye MF, Zhang ZX, Tao F, Zhang Y. Cytokine release syndrome triggered by programmed death 1 blockade (sintilimab) therapy in a psoriasis patient: A case report. *World J Clin Cases* 2024; **12**: 3555-3560 [PMID: 38983424 DOI: 10.12998/wjcc.v12.i18.3555]
8 **Sahu M**, Suryawanshi H. Immunotherapy: The future of cancer treatment. *J Oral Maxillofac Pathol* 2021; **25**: 371 [PMID: 34703141 DOI: 10.4103/0973-029X.325257]
9 **Cappell KM**, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol* 2023; **20**: 359-371 [PMID: 37055515 DOI: 10.1038/s41571-023-00754-1]
10 **Laskowski T**, Rezvani K. Adoptive cell therapy: Living drugs against cancer. *J Exp Med* 2020; **217** [PMID: 33227136 DOI: 10.1084/jem.20200377]
11 **Zhang Y**, Zheng J. Functions of Immune Checkpoint Molecules Beyond Immune Evasion. *Adv Exp Med Biol* 2020; **1248**: 201-226 [PMID: 32185712 DOI: 10.1007/978-981-15-3266-5_9]
12 **Guo Z**, Zhang R, Yang AG, Zheng G. Diversity of immune checkpoints in cancer immunotherapy. *Front Immunol* 2023; **14**: 1121285 [PMID:

36960057 DOI: 10.3389/fimmu.2023.1121285]
13 **Gaikwad S**, Agrawal MY, Kaushik I, Ramachandran S, Srivastava SK. Immune checkpoint proteins: Signaling mechanisms and molecular interactions in cancer immunotherapy. *Semin Cancer Biol* 2022; **86**: 137-150 [PMID: 35341913 DOI: 10.1016/j.semcancer.2022.03.014]
14 **Buchbinder EI**, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. *Am J Clin Oncol* 2016; **39**: 98-106 [PMID: 26558876 DOI: 10.1097/COC.0000000000000239]
15 **Seidel JA**, Otsuka A, Kabashima K. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. *Front Oncol* 2018; **8**: 86 [PMID: 29644214 DOI: 10.3389/fonc.2018.00086]
16 **Shiravand Y**, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, Ladwa R, O'Byrne K, Kulasinghe A. Immune Checkpoint Inhibitors in Cancer Therapy. *Curr Oncol* 2022; **29**: 3044-3060 [PMID: 35621637 DOI: 10.3390/curroncol29050247]
17 **Les I**, Martínez M, Pérez-Francisco I, Cabero M, Teijeira L, Arrazubi V, Torrego N, Campillo-Calatayud A, Elejalde I, Kochan G, Escors D. Predictive Biomarkers for Checkpoint Inhibitor Immune-Related Adverse Events. *Cancers (Basel)* 2023; **15** [PMID: 36900420 DOI: 10.3390/cancers15051629]
18 **Choi J**, Lee SY. Clinical Characteristics and Treatment of Immune-Related Adverse Events of Immune Checkpoint Inhibitors. *Immune Netw* 2020; **20**: e9 [PMID: 32158597 DOI: 10.4110/in.2020.20.e9]
19 **Wang SJ**, Dougan SK, Dougan M. Immune mechanisms of toxicity from checkpoint inhibitors. *Trends Cancer* 2023; **9**: 543-553 [PMID: 37117135 DOI: 10.1016/j.trecan.2023.04.002]
20 **Johnson DB**, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022; **19**: 254-267 [PMID: 35082367 DOI: 10.1038/s41571-022-00600-w]
21 **Okiyama N**, Tanaka R. Immune-related adverse events in various organs caused by immune checkpoint inhibitors. *Allergol Int* 2022; **71**: 169-178 [PMID: 35101349 DOI: 10.1016/j.alit.2022.01.001]
22 **Popa LG**, Giurcaneanu C, Portelli MG, Mihai MM, Beiu C, Orzan OA, Ion A, Anghel TH. Perspectives on Psoriasiform Adverse Events from Immune Checkpoint Inhibitors: Lessons Learned from Our Practice. *Medicina (Kaunas)* 2024; **60** [PMID: 38541099 DOI: 10.3390/medicina60030373]
23 **Zhang X**, Fu Z, Yan C. Cytokine release syndrome induced by pembrolizumab: A case report. *Medicine (Baltimore)* 2022; **101**: e31998 [PMID: 36626467 DOI: 10.1097/MD.0000000000031998]
24 **Tay SH**, Toh MMX, Thian YL, Vellayappan BA, Fairhurst AM, Chan YH, Aminkeng F, Bharwani LD, Huang Y, Mak A, Wong ASC. Cytokine Release Syndrome in Cancer Patients Receiving Immune Checkpoint Inhibitors: A Case Series of 25 Patients and Review of the Literature. *Front Immunol* 2022; **13**: 807050 [PMID: 35154124 DOI: 10.3389/fimmu.2022.807050]
25 **Martins F**, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, Shabafrouz K, Ribi C, Cairoli A, Guex-Crosier Y, Kuntzer T, Michielin O, Peters S, Coukos G, Spertini F, Thompson JA, Obeid M. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 2019; **16**: 563-580 [PMID: 31092901 DOI: 10.1038/s41571-019-0218-0]
26 **Eggermont AM**, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, Hamid O, Robert C, Ascierto PA, Richards JM, Lebbé C, Ferraresi V, Smylie M, Weber JS, Maio M, Bastholt L, Mortier L, Thomas L, Tahir S, Hauschild A, Hassel JC, Hodi FS, Taitt C, de Pril V, de Schaetzen G, Suciu S, Testori A. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. *N Engl J Med* 2016; **375**: 1845-1855 [PMID: 27717298 DOI: 10.1056/NEJMoa1611299]
27 **Weber JS**, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012; **30**: 2691-2697 [PMID: 22614989 DOI: 10.1200/JCO.2012.41.6750]
28 **Gelao L**, Criscitiello C, Esposito A, Goldhirsch A, Curigliano G. Immune checkpoint blockade in cancer treatment: a double-edged sword cross-targeting the host as an "innocent bystander". *Toxins (Basel)* 2014; **6**: 914-933 [PMID: 24594636 DOI: 10.3390/toxins6030914]
29 **Postow MA**, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, Meyer N, Giguere JK, Agarwala SS, Shaheen M, Ernstoff MS, Minor D, Salama AK, Taylor M, Ott PA, Rollin LM, Horak C, Gagnier P, Wolchok JD, Hodi FS. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med* 2015; **372**: 2006-2017 [PMID: 25891304 DOI: 10.1056/NEJMoa1414428]
30 **García Roche A**, Díaz Lagares C, Élez E, Ferrer Roca R. Cytokine release syndrome. Reviewing a new entity in the intensive care unit. *Med Intensiva (Engl Ed)* 2019; **43**: 480-488 [PMID: 30922608 DOI: 10.1016/j.medin.2019.01.009]
31 **Cosenza M**, Sacchi S, Pozzi S. Cytokine Release Syndrome Associated with T-Cell-Based Therapies for Hematological Malignancies: Pathophysiology, Clinical Presentation, and Treatment. *Int J Mol Sci* 2021; **22** [PMID: 34299273 DOI: 10.3390/ijms22147652]
32 **Shah D**, Soper B, Shopland L. Cytokine release syndrome and cancer immunotherapies - historical challenges and promising futures. *Front Immunol* 2023; **14**: 1190379 [PMID: 37304291 DOI: 10.3389/fimmu.2023.1190379]
33 **Xing X**, Hu X. Risk factors of cytokine release syndrome: stress, catecholamines, and beyond. *Trends Immunol* 2023; **44**: 93-100 [PMID: 36586780 DOI: 10.1016/j.it.2022.12.003]
34 **Morris G**, Bortolasci CC, Puri BK, Marx W, O'Neil A, Athan E, Walder K, Berk M, Olive L, Carvalho AF, Maes M. The cytokine storms of COVID-19, H1N1 influenza, CRS and MAS compared. Can one sized treatment fit all? *Cytokine* 2021; **144**: 155593 [PMID: 34074585 DOI: 10.1016/j.cyto.2021.155593]
35 **Mansouri V**, Yazdanpanah N, Rezaei N. The immunologic aspects of cytokine release syndrome and graft versus host disease following CAR T cell therapy. *Int Rev Immunol* 2022; **41**: 649-668 [PMID: 34607523 DOI: 10.1080/08830185.2021.1984449]
36 **Hsiao M**, Akhtari M, Wang LY. Investigating the Relationship between Cytokine Release Syndrome, Graft-Versus-Host Disease, and One-Year Mortality after Haploidentical Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Tr* 2019; **25**: S216 [DOI: 10.1016/j.bbmt.2018.12.296]
37 **Ceschi A**, Noseda R, Palin K, Verhamme K. Immune Checkpoint Inhibitor-Related Cytokine Release Syndrome: Analysis of WHO Global Pharmacovigilance Database. *Front Pharmacol* 2020; **11**: 557 [PMID: 32425791 DOI: 10.3389/fphar.2020.00557]
38 **Van De Vyver AJ**, Marrer-Berger E, Wang K, Lehr T, Walz AC. Cytokine Release Syndrome By T-cell-Redirecting Therapies: Can We Predict and Modulate Patient Risk? *Clin Cancer Res* 2021; **27**: 6083-6094 [PMID: 34162679 DOI: 10.1158/1078-0432.CCR-21-0470]
39 **Frey N**, Porter D. Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy. *Biol Blood Marrow Transplant* 2019; **25**: e123-e127 [PMID: 30586620 DOI: 10.1016/j.bbmt.2018.12.756]
40 **Yildizhan E**, Kaynar L. Cytokine release syndrome. *J Oncol Sci* 2018; **4**: 134-141 [DOI: 10.1016/j.jons.2018.09.002]
41 **Gödel P**, Shimabukuro-Vornhagen A, von Bergwelt-Baildon M. Understanding cytokine release syndrome. *Intensive Care Med* 2018; **44**: 371-373 [PMID: 28956093 DOI: 10.1007/s00134-017-4943-5]
42 **Shimabukuro-Vornhagen A**, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B, von Bergwelt-Baildon

MS. Cytokine release syndrome. *J Immunother Cancer* 2018; **6**: 56 [PMID: 29907163 DOI: 10.1186/s40425-018-0343-9]

43 **Armstrong AW**, Patel M, Li C, Garg V, Mandava MR, Wu JJ. Real-world switching patterns and associated characteristics in patients with psoriasis treated with biologics in the United States. *J Dermatolog Treat* 2023; **34**: 2200870 [PMID: 37154473 DOI: 10.1080/09546634.2023.2200870]

44 **Xu X**, Zhang HY. The Immunogenetics of Psoriasis and Implications for Drug Repositioning. *Int J Mol Sci* 2017; **18** [PMID: 29292715 DOI: 10.3390/ijms18122650]

45 **Man AM**, Orăsan MS, Hoteiuc OA, Olănescu-Vaida-Voevod MC, Mocan T. Inflammation and Psoriasis: A Comprehensive Review. *Int J Mol Sci* 2023; **24** [PMID: 38003284 DOI: 10.3390/ijms242216095]

46 **Liang Y**, Sarkar MK, Tsoi LC, Gudjonsson JE. Psoriasis: a mixed autoimmune and autoinflammatory disease. *Curr Opin Immunol* 2017; **49**: 1-8 [PMID: 28738209 DOI: 10.1016/j.coi.2017.07.007]

47 **Kölliker Frers R**, Otero-Losada M, Kobiec T, Herrera MI, Udovin L, Kusnier CF, Capani F. Interleukin-1 Links Autoimmune and Autoinflammatory Pathophysiology in Mixed-Pattern Psoriasis. *Mediators Inflamm* 2021; **2021**: 2503378 [PMID: 34697538 DOI: 10.1155/2021/2503378]

48 **Chen L**, Li J, Zhu W, Kuang Y, Liu T, Zhang W, Chen X, Peng C. Skin and Gut Microbiome in Psoriasis: Gaining Insight Into the Pathophysiology of It and Finding Novel Therapeutic Strategies. *Front Microbiol* 2020; **11**: 589726 [PMID: 33384669 DOI: 10.3389/fmicb.2020.589726]

49 **Sieminska I**, Pieniawska M, Grzywa TM. The Immunology of Psoriasis-Current Concepts in Pathogenesis. *Clin Rev Allergy Immunol* 2024; **66**: 164-191 [PMID: 38642273 DOI: 10.1007/s12016-024-08991-7]

50 **Constantin MM**, Bucur S, Mutu CC, Poenaru E, Olteanu R, Ionescu RA, Nicolescu AC, Furtunescu F, Constantin T. The Impact of Smoking on Psoriasis Patients with Biological Therapies in a Bucharest Hospital. *J Pers Med* 2021; **11** [PMID: 34442396 DOI: 10.3390/jpm11080752]

51 **Kamiya K**, Kishimoto M, Sugai J, Komine M, Ohtsuki M. Risk Factors for the Development of Psoriasis. *Int J Mol Sci* 2019; **20** [PMID: 31491865 DOI: 10.3390/ijms20184347]

52 **Olejniczak-Staruch I**, Ciążyńska M, Sobolewska-Sztychny D, Narbutt J, Skibińska M, Lesiak A. Alterations of the Skin and Gut Microbiome in Psoriasis and Psoriatic Arthritis. *Int J Mol Sci* 2021; **22** [PMID: 33924414 DOI: 10.3390/ijms22083998]

53 **Mirghani H**, Altemani AT, Altemani ST, Alhatlani JAA, Alsulaimani NMI, AlHuraish DSA, Al Mudhi AHA, Ghabban WJR, Alanazi AH, Alamrani BA. The Cross Talk Between Psoriasis, Obesity, and Dyslipidemia: A Meta-Analysis. *Cureus* 2023; **15**: e49253 [PMID: 38143624 DOI: 10.7759/cureus.49253]

54 **Gratton R**, Del Vecchio C, Zupin L, Crovella S. Unraveling the Role of Sex Hormones on Keratinocyte Functions in Human Inflammatory Skin Diseases. *Int J Mol Sci* 2022; **23** [PMID: 35328552 DOI: 10.3390/ijms23063132]

55 **Liu S**, He M, Jiang J, Duan X, Chai B, Zhang J, Tao Q, Chen H. Triggers for the onset and recurrence of psoriasis: a review and update. *Cell Commun Signal* 2024; **22**: 108 [PMID: 38347543 DOI: 10.1186/s12964-023-01381-0]

56 **Sobolev V**, Soboleva A, Denisova E, Denieva M, Dvoryankova E, Suleymanov E, Zhukova OV, Potekaev N, Korsunskaya I, Mezentsev A. Differential Expression of Estrogen-Responsive Genes in Women with Psoriasis. *J Pers Med* 2021; **11** [PMID: 34575702 DOI: 10.3390/jpm11090925]

57 **Yamazaki F**. Psoriasis: Comorbidities. *J Dermatol* 2021; **48**: 732-740 [PMID: 33763899 DOI: 10.1111/1346-8138.15840]

58 **Liang H**, Li J, Zhang K. Pathogenic role of S100 proteins in psoriasis. *Front Immunol* 2023; **14**: 1191645 [PMID: 37346040 DOI: 10.3389/fimmu.2023.1191645]

59 **Kolbinger F**, Loesche C, Valentin MA, Jiang X, Cheng Y, Jarvis P, Peters T, Calonder C, Bruin G, Polus F, Aigner B, Lee DM, Bodenlenz M, Sinner F, Pieber TR, Patel DD. β-Defensin 2 is a responsive biomarker of IL-17A-driven skin pathology in patients with psoriasis. *J Allergy Clin Immunol* 2017; **139**: 923-932.e8 [PMID: 27502297 DOI: 10.1016/j.jaci.2016.06.038]

60 **Grän F**, Kerstan A, Serfling E, Goebeler M, Muhammad K. Current Developments in the Immunology of Psoriasis. *Yale J Biol Med* 2020; **93**: 97-110 [PMID: 32226340]

61 **Armstrong AW**, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *JAMA* 2020; **323**: 1945-1960 [PMID: 32427307 DOI: 10.1001/jama.2020.4006]

62 **Tokuyama M**, Mabuchi T. New Treatment Addressing the Pathogenesis of Psoriasis. *Int J Mol Sci* 2020; **21** [PMID: 33050592 DOI: 10.3390/ijms21207488]

63 **Antal D**, Alimohammadi S, Bai P, Szöllősi AG, Szántó M. Antigen-Presenting Cells in Psoriasis. *Life (Basel)* 2022; **12** [PMID: 35207521 DOI: 10.3390/life12020234]

64 **Boutet MA**, Nerviani A, Gallo Afflitto G, Pitzalis C. Role of the IL-23/IL-17 Axis in Psoriasis and Psoriatic Arthritis: The Clinical Importance of Its Divergence in Skin and Joints. *Int J Mol Sci* 2018; **19** [PMID: 29425183 DOI: 10.3390/ijms19020530]

65 **Conrad C**, Gilliet M. Psoriasis: from Pathogenesis to Targeted Therapies. *Clin Rev Allergy Immunol* 2018; **54**: 102-113 [PMID: 29349534 DOI: 10.1007/s12016-018-8668-1]

66 **Lowes MA**, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol* 2014; **32**: 227-255 [PMID: 24655295 DOI: 10.1146/annurev-immunol-032713-120225]

67 **Schön MP**. Adaptive and Innate Immunity in Psoriasis and Other Inflammatory Disorders. *Front Immunol* 2019; **10**: 1764 [PMID: 31402919 DOI: 10.3389/fimmu.2019.01764]

68 **Milavec-Puretić V**, Mance M, Ceović R, Lipozenčić J. Drug induced psoriasis. *Acta Dermatovenerol Croat* 2011; **19**: 39-42 [PMID: 21489366 DOI: 10.4103/0973-3698.272159]

69 **Balak DM**, Hajdarbegovic E. Drug-induced psoriasis: clinical perspectives. *Psoriasis (Auckl)* 2017; **7**: 87-94 [PMID: 29387611 DOI: 10.2147/PTT.S126727]

70 **Lu J**, Lu Y. Paradoxical psoriasis: The flip side of idiopathic psoriasis or an autocephalous reversible drug reaction? *J Transl Autoimmun* 2023; **7**: 100211 [PMID: 37731549 DOI: 10.1016/j.jtauto.2023.100211]

71 **Vasconcellos JB**, Pereira DD, Vargas TJ, Levy RA, Pinheiro GD, Cursi ÍB. Paradoxical psoriasis after the use of anti-TNF in a patient with rheumatoid arthritis. *An Bras Dermatol* 2016; **91**: 137-139 [PMID: 28300922 DOI: 10.1590/abd1806-4841.20164456]

72 **Morelli M**, Carbone ML, Scaglione GL, Scarponi C, Di Francesco V, Pallotta S, De Galitiis F, Rahimi S, Madonna S, Failla CM, Albanesi C. Identification of immunological patterns characterizing immune-related psoriasis reactions in oncological patients in therapy with anti-PD-1 checkpoint inhibitors. *Front Immunol* 2024; **15**: 1346687 [PMID: 38495872 DOI: 10.3389/fimmu.2024.1346687]

73 **Sánchez-Martínez E**, Sáez-Belló M, Ochenduszko S, Mateu-Puchades A. Psoriasis and Anti-PD-1 and Anti-PD-L1 Immunotherapy: Three Cases, a Review of the Literature, and a Proposed Management Algorithm. *Actas Dermosifiliogr* 2022; **113**: 427-431 [PMID: 35623735 DOI:

10.1016/j.ad.2020.05.017]

74 **Kuszczak B**, Wróbel T, Wicherska-Pawłowska K, Rybka J. The Role of BCL-2 and PD-1/PD-L1 Pathway in Pathogenesis of Myelodysplastic Syndromes. *Int J Mol Sci* 2023; **24** [PMID: 36902139 DOI: 10.3390/ijms24054708]

75 **Wan Z**, Huang J, Ou X, Lou S, Wan J, Shen Z. Psoriasis de novo or exacerbation by PD-1 checkpoint inhibitors. *An Bras Dermatol* 2024; **99**: 425-432 [PMID: 38388337 DOI: 10.1016/j.abd.2023.09.003]

76 **Zhang Y**, Wen X, OuYang Y, Hu Y, Fang X, Zhang J, Yuan Y. Severe cytokine release syndrome induced by immune checkpoint inhibitors in cancer patients - A case report and review of the literature. *Heliyon* 2024; **10**: e24380 [PMID: 38293388 DOI: 10.1016/j.heliyon.2024.e24380]

77 **Tanaka R**, Ichimura Y, Kubota N, Saito A, Nakamura Y, Ishitsuka Y, Watanabe R, Fujisawa Y, Kanzaki M, Mizuno S, Takahashi S, Fujimoto M, Okiyama N. Activation of CD8 T cells accelerates anti-PD-1 antibody-induced psoriasis-like dermatitis through IL-6. *Commun Biol* 2020; **3**: 571 [PMID: 33060784 DOI: 10.1038/s42003-020-01308-2]

78 **Alves NRM**, Kurizky PS, da Mota LMH, de Albuquerque CP, Esper JT, Campos ASC, Reis VP, Ferro HM, Gil-Jaramillo N, Brito-de-Sousa JP, Leal LCL, Nóbrega OT, Araújo CN, Santos Júnior ACMD, Martins GA, Martins Filho OA, Gomes CM. Elevated serum IL-6 levels predict treatment interruption in patients with moderate to severe psoriasis: a 6-year real-world cohort study. *An Bras Dermatol* 2024; **99**: 34-42 [PMID: 37634972 DOI: 10.1016/j.abd.2023.03.002]

79 **Wang M**, Zhai X, Li J, Guan J, Xu S, Li Y, Zhu H. The Role of Cytokines in Predicting the Response and Adverse Events Related to Immune Checkpoint Inhibitors. *Front Immunol* 2021; **12**: 670391 [PMID: 34367136 DOI: 10.3389/fimmu.2021.670391]

80 **Singh R**, Koppu S, Perche PO, Feldman SR. The Cytokine Mediated Molecular Pathophysiology of Psoriasis and Its Clinical Implications. *Int J Mol Sci* 2021; **22** [PMID: 34884596 DOI: 10.3390/ijms222312793]

81 **Voudouri D**, Nikolaou V, Laschos K, Charpidou A, Soupos N, Triantafyllopoulou I, Panoutsopoulou I, Aravantinos G, Syrigos K, Stratigos A. Anti-PD1/PDL1 induced psoriasis. *Curr Probl Cancer* 2017; **41**: 407-412 [PMID: 29096940 DOI: 10.1016/j.currproblcancer.2017.10.003]

82 **Yan BX**, Chen XY, Ye LR, Chen JQ, Zheng M, Man XY. Cutaneous and Systemic Psoriasis: Classifications and Classification for the Distinction. *Front Med (Lausanne)* 2021; **8**: 649408 [PMID: 34722555 DOI: 10.3389/fmed.2021.649408]

83 **Apalla Z**, Nikolaou V, Fattore D, Fabbrocini G, Freites-Martinez A, Sollena P, Lacouture M, Kraehenbuehl L, Stratigos A, Peris K, Lazaridou E, Richert B, Vigarios E, Riganti J, Baroudjian B, Filoni A, Dodiuk-Gad R, Lebbé C, Sibaud V. European recommendations for management of immune checkpoint inhibitors-derived dermatologic adverse events. The EADV task force 'Dermatology for cancer patients' position statement. *J Eur Acad Dermatol Venereol* 2022; **36**: 332-350 [PMID: 34910332 DOI: 10.1111/jdv.17855]

84 **Rodríguez-jiménez P**, Ibarguren AM, Butrón-bris B, Martos-cabrera L, Llamas-velasco M. Can we treat anti-PD1 induced psoriasis in patients with active cancer with biologic therapy? Report of three cases. *JEADV Clin Pract* 2023; **2**: 379-381 [DOI: 10.1002/jvc2.130]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6791-6807

DOI: 10.12998/wjcc.v12.i35.6791

ISSN 2307-8960 (online)

REVIEW

Acellular dermal matrices in reconstructive surgery; history, current implications and future perspectives for surgeons

Ömer F Dilek, Kamuran Z Sevim, Osman N Dilek

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 A

P-Reviewer: Ahmed F

Received: May 27, 2024
Revised: October 3, 2024
Accepted: October 15, 2024
Published online: December 16, 2024
Processing time: 149 Days and 22.1 Hours

Ömer F Dilek, Department of Plastic, Reconstructive and Aesthetic Surgery, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul 34396, Türkiye

Kamuran Z Sevim, Department of Plastic and Reconstructive Surgery, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul 34396, Türkiye

Osman N Dilek, Department of Surgery, İzmir Katip Celebi University, School of Medicine, İzmir 35150, Türkiye

Corresponding author: Ömer F Dilek, MD, Assistant Professor, Department of Plastic, Reconstructive and Aesthetic Surgery, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, 34396, Sarıyer, İstanbul 34396, Türkiye. ofdilek@gmail.com

Abstract

Large-scale defects of body in the reconstructive surgical practice, and the helplessness of their repair with autologous tissues, have been an important factor in the development of artificial biological products for the temporary, definitive, or staged repair of these defects. A major advance in the field of plastic and other reconstructive surgery in this regard has been the introduction and successful use of acellular dermal matrices (ADMs). In recent years, not only the type of tissue from which ADMs are produced, product range, diversity and areas of use have increased, but their use in reconstructive fields, especially in post oncologic breast surgery, has become highly regarded and this has favored ADMs to be a potential cornerstone in specific and well-defined surgical fields in future. It is essential that reconstructive surgeons become familiar with some of the ADM's as well as the advantages and limitations to their use. This review not only provides basic science and clinical evidence of the current use of ADMs in wide range of surgical fields but also targets to keep them as an important backdrop in the armamentarium of reconstructive surgeons. Brief considerations of possible future directions for ADMs are also conducted in the end.

Key Words: Acellular dermal matrices; Breast; Decellularization; Reconstruction; Surgery; Tissue defect

Core Tip: The use of acellular dermal matrix in parotid tumor surgery can reduce the incidence of Frey syndrome, especially when the diameter of the surgically removed parotid tissue is greater than 4 cm. This review not only provides basic science and clinical evidence of the current use of acellular dermal matrices in wide range of surgical fields but also targets to keep them as an important backdrop in the armamentarium of reconstructive surgeons.

Citation: Dilek ÖF, Sevim KZ, Dilek ON. Acellular dermal matrices in reconstructive surgery; history, current implications and future perspectives for surgeons. *World J Clin Cases* 2024; 12(35): 6791-6807
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6791.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6791

INTRODUCTION

Normal wound healing is a dynamic process that involves the restoration of the skin's barrier function and mechanical and functional integrity. This process involves interactions of the cells with their non-cellular microenvironment called extracellular matrix (ECM) *via* complex protein-mediated signaling pathways. ECM interactions of the cellular fraction of the wound bed direct them to differentiate or dedifferentiate, proliferate, or remain quiescent, and assume the architecture and function of the skin or other organ tissues[1]. Although, fundamentally, the ECM is composed of water, proteins, proteoglycans, hyaluronic acid, collagen, and elastin, each tissue has an ECM with a unique composition and topology that is generated during tissue regeneration through a dynamic and reciprocal dialogue with the cellular fractions. Through these topologies and unique characteristics, the ECM generates the biochemical and mechanical properties of each organ, such as its tensile and compressive strength and elasticity, and also mediates protection by a buffering action that maintains extracellular homeostasis and water retention[1].

In chronic wounds, the ECM is often damaged or depleted to the extent that it can no longer adequately support healing through cellular interactions[2]. This usually results from inflammatory and proteolytic environment of chronic wounds. A high ratio of protease-to-protease inhibitors indeed, has been a well-shown mechanism for degradation of ECM, growth factors and growth factor receptors in chronic wounds[2].

Large-scale traumatic wounds of the body on the other hand, despite the numerous improvements of the flap number and choices, still remain as a major challenge for the reconstructive surgeons. Additionally, each of these reconstructive options has disadvantages such as donor site morbidity, risk of flap/graft complications or even failure. In some cases, such as excessive wound depth or specialized function of tissue needing repair, patient and/or wound characteristics may preclude the use of traditional techniques for soft-tissue coverage as well[3].

The inability of the repair of various wounds with autologous tissues, have been an important factor in the development of artificial biomaterials for the temporary, definitive, or staged repair of the large defects and the defects that lack appropriate well-vascularized soft tissue elements for grafting, such as wounds with exposed bone, cartilage, and tendon. The terms biomaterials, biologic scaffolds, bioprosthetic, and biologic matrices are used interchangeably and represent a diverse continuum of engineered products that serve as scaffolds which interact with native tissue, promoting vascular and cytologic ingrowth[4,5], cell propagation, migration, and differentiation[6]. A major advance in the field of plastic and other reconstructive surgery in this regard has been the introduction and successful use of acellular dermal matrices (ADMs).

MECHANISM OF ADM

In simple terms, ADMs are biological membranes that are free of cellular components and other antigenic structures, where immunogenicity is no longer an issue. When ADMs are placed in the wound, host cells are incorporated into the matrix and directed by preserved growth factors and mechanical signals in the matrix structure[6,7]. A variety of host cells invade the ADM[4,5], including fibroblasts, myofibroblasts, lymphocytes, macrophages, granulocytes, mast cells and others[7]. After inflammatory cell infiltration, the matrix undergoes remodeling[7], collagen and elastin levels increase, and revascularization is initiated[4,5-8]. Essentially, the ADM acts as a scaffold to promote host tissue growth[3]. These processes not only make ADM a well vascularized graft bed, but also render a durable, relatively thicker barrier, paving the way for its use where anatomical layers need to be kept apart, or soft tissues need to be reinforced.

ADMs can be derived either from donated skin and other organs (allograft or from animals such as swine or cattle xenograft). The process of removing cells from tissues and organs is known as decellularization that has been described extensively in the literature[9,10]. More briefly, decellularization has been performed through chemical, physical, enzymatic, or combinative methods. As the most important step, it strictly aims minimal disruption of the 3-D structure of the ECM of tissues so that the method must be individualized for each tissue characteristics[11]. However, complete removal of all cell remnants may not always be completely possible, and decellularization processes inevitably and invariably cause some degree of disruption of matrix architecture which leads the seek for more perfection of these steps by the researchers and industry[10]. Next steps include decontamination of the chemicals, optional cross-linking, quality analysis of the remaining ECM scaffold, sterilization, packaging, and preservation for marketing[12,13] (Figure 1).

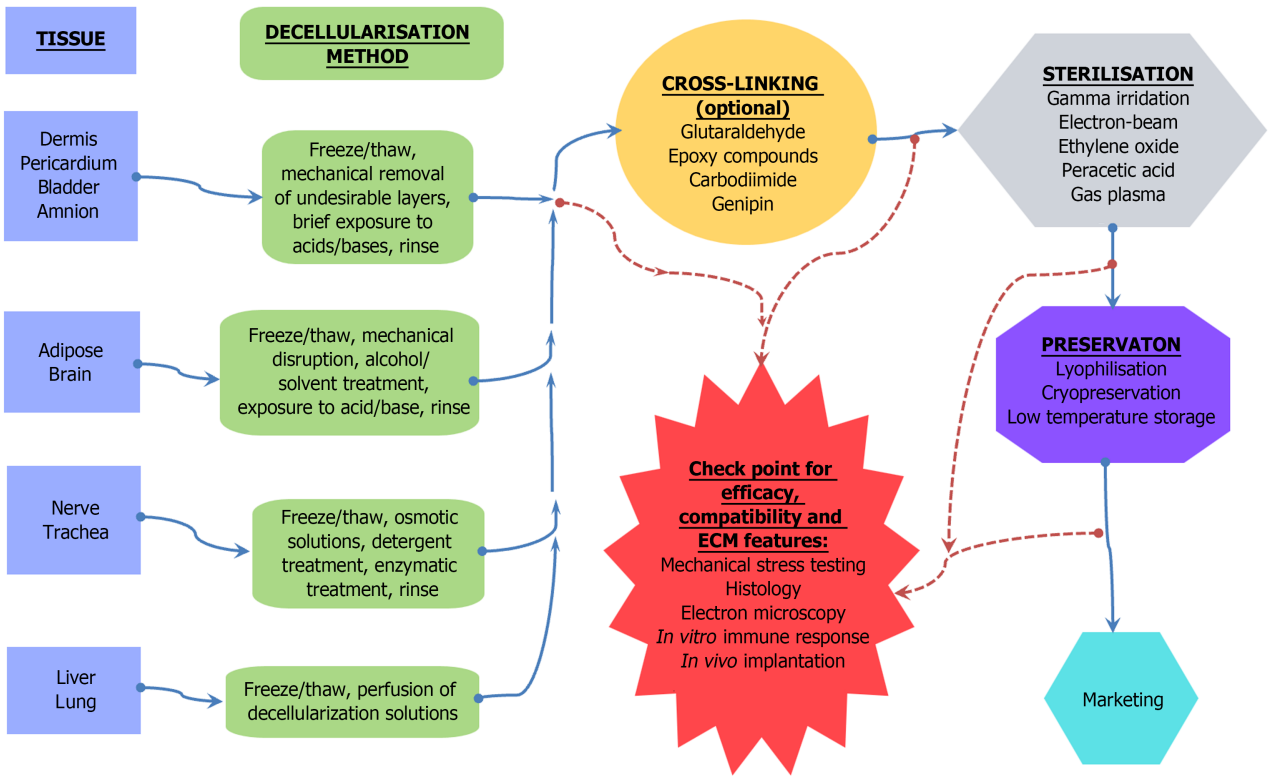

Figure 1 The flowchart summarizes the techniques commonly used in the process of obtaining acellular dermal matrix from a variety of tissues. ECM: Extracellular matrix.

Tissue from which the antigenic content has been removed has now become a cell-free scaffold containing ECM elements[4,5] such as collagen, fibronectin, elastin, laminin, glycosaminoglycans and hyaluronic acid as well as some growth factors. This 3-D acellular collagenous mesh scaffold without immunogenicity can be now gradually *de novo* revitalized by autologous cells after implantation. Indeed, many studies have shown that cell-free ECM scaffolds are capable of promoting proliferation[6,7], growth[6], and differentiation[6,7] of many kinds of cell populations in vitro[4,5,7,8], as well as inducing structural tissue remodeling processes after transplantation in humans[6,14-17]. Therefore, the use of 3-D ADM meshes derived from tissues is an increasingly used method in reconstructive surgery, regenerative medicine, and bioengineering.

It is not always possible for surgeons to accurately estimate the amount of tissue to be mobilized or to accurately predict the laxity, vascularity, access limits or arc of rotation of these tissues before surgery. In addition, sometimes the size of the defect may be larger, or the tension of the repaired anatomical layers may be higher than predicted. Undoubtedly, every surgeon will appreciate the availability of ADMs as reliable members of the bench, which always have the potential to offer a quick, staged, temporary or permanent solution alternatives to such, unexpected problems. Furthermore, although such the advantages of ADMs for each clinical area of use may vary, it is clear that another great advantage is the elimination of donor site morbidity and related operative efforts, such as pursuit for neighboring soft tissue, which should be loose, well vascularized, and abundant or preparation for another operative field for graft harvest.

CHALLENGES AND LIMITATIONS

ADM's are still foreign and possess the risk of rejection[13,17] and disease transmission[13,14]. Furthermore, the classic risks of complications associated with autologous reconstructions, such as infection, necrosis, seroma, and failed engraftment still apply to ADMs. Moreover, patients belonging to certain ethnic and/or religious groups may hold beliefs that preclude the use of products with certain tissue origins. For example, although there are views that the use of pig-derived biologics is permitted in Islam[18], Christianity[19] and Judaism[20] under certain conditions, these have not become consensuses that are readily accepted by all sub-fractions. Also, the vegan perspective[21] strongly opposes the use of animals as organ donors and emphasizes the need to develop animal-free alternatives. On the other hand, the perception that ADM is expensive is often ingrained in surgeons and indeed, ADM can be a reasonable choice for only some patients among various healthcare systems when it comes to the standard product costs ranging from several hundred to thousands of dollars. Nevertheless, given the overall clinical context, risks, complications and outcomes compared to alternative conventional treatments, some authors have advocated[22-25] evidence of cost-effectiveness, while other studies have found ADMs not to be cost-effective[26-28]. Some authors also probed the associations between

ADM-related publication, industry funding, funding disclosure, and public interest and criticized the objectivity of the reports in regard with the strong correlation between them[29].

Table 1 provides some examples of ADMs on the market. However, the options are more numerous, and their advantages or differences are often subtle. Things to consider when making a choice include the source, cross-linking, how it is stored, whether it requires a rehydration period before implantation, the method of sterilization, how it can be stretched *in vitro* and so on. The following sections provide examples of the wide range of uses of ADMs in plastic and reconstructive surgery, from head to toe, from visible to visceral, and list the main exemplary articles for each region. Indications and techniques are not absolute and are intended to give the surgeon discretion from a broader perspective.

CLINICAL APPLICATIONS

Burns

Reconstruction of skin continuity after a severe burn is crucial for healing. Reconstruction after a severe burn injury also involves healing of the skin's natural elasticity, texture, and contour. Complete destruction of the skin requires the use of a skin substitute. The method of choice is a graft consisting of the epidermis and a super thin layer of dermis. It is important to rebuild and replace this tissue to achieve good epithelial coverage. The optimal method of treating extensive full-thickness or deep dermal skin burns is split-thickness skin grafts. However, in extensive burn conditions autologous donor skin sources are often scarce and skin grafts can fall short in providing stable coverage to restore the structure and function of skin. Moreover, the debrided defective area may not yet be ready to form a good bed for grafting and grafts taken limited harvest sites may not contain sufficient dermal thickness. In the face of these difficulties in burn conditions, ADMs were initially used successfully in combination with a thin partial thickness skin graft to cover full thickness burn defects[30], and then expanded their use as a useful adjunct to promote secondary healing or provide temporary wound coverage in deep dermal burns[31-35]. Later, the already widespread use of ADMs and the accumulating clinical evidence in the field of burns (Table 2) make them an important tool not only for extensive burns where surgeons are helpless, but also in situations where it is desirable to reduce or prevent contracture, scarring and poor wound healing[36-40]. Until recently, a few long-term high-quality studies evaluated the use of ADMs in burns and supported the positive results obtained up to that time, showing that the use of ADMs improves scar quality[41-43] and that their use around the joint[44] may be advantageous. Randomized controlled trials also advocated that ADM used in acute extensive burns are associated with rapid healing[45,47], better function[45,46] and higher quality of life[46,47]. However, more recently, a growing number of randomized controlled trials have revealed some conflicting data with these frequently reported positive results. Almeida *et al*[48] reported no significant difference in scar quality, clinical and biomechanical characteristics between 3 different ADM products and split thickness skin grafts at the end of 1 year. Another similar structured study[49] reported that burn contractures reconstructed using ADM had a significantly higher rate of recurrence at 12 months. In both two studies, however, the sample groups consisted of contracture patients rather than acute burn patients. Gardien *et al*[50] also reported no significant difference in scar quality between the ADM and non-ADM groups at 6 years in a population of 24 patients. As more well-planned and larger sample randomized controlled trials are conducted, we will be able to better understand the limitations and benefits of ADMs in burns. However, the data on the safety of ADMs in burns is uncontroversial and their role in reducing the need for donor sites, especially in extensive burns, will probably ensure that they will remain irreplaceable for longer periods.

Chronic wounds

Wounds that are difficult to heal, contain exposed bone, tendons or are infected are frequently encountered by plastic surgeons and other related sub-disciplines. Replacing the defective dermis using ADMs instead of performing reconstructions with long operative time, several steps, long hospitalization or large donor site morbidities has made ADMs, which have proven their efficacy in burns, an important backup tool for surgeons, especially in the elderly and comorbid population or patients undergone repeated failed reconstructive attempts. Despite the paucity of high-quality data, the overwhelming body of literature, consisting of numerous case reports or case series, should be kept in mind by reconstructive surgeons and ADMs should be considered as an option as a lifeboat in well-considered, well-planned and well-selected cases. Table 3 provides examples of the use of ADMs in the management of a wide range of difficult wounds.

Besides good quality clinical evidence indicating the efficacy[52,53] of ADM in diabetic foot ulcer (DFU), it bears highest number of randomized controlled trials among chronic wounds[54-56]. Hu *et al*[54] found 46.2%, 69.2%, and 88.5% rates of complete wound closure in the ADM + skin grafting group at 2, 4- and 8-weeks post-grafting, respectively. These were not significantly different from those of the control (only skin grafting) group (61.5%, 76.9%, and 84.6%) at each timepoint. However, the recurrence rate during the follow-up period (12 months) was significantly lower in the experimental group compared with the control group. Authors concluded that combining skin graft on top of an ADM is a safe, effective and favorable option for treating DFUs and it may improve the quality of life of patients with DFUs by reducing the risk of amputation and recurrence. Zelen *et al*[55] in their prospective, randomized, controlled, multicenter follow-up trial, found significantly higher healing ratio in ADM + standard of care (SOC) group compared to SOC alone group at 12 weeks. They also associated rapid healing time with low costs when compared to other treatment modalities. Current data revealed that compared with SOC, acellular dermal matrix may accelerate the healing velocity of uninfected, non-ischemic, full-thickness DFU[57]. It also seems to have superiority in generating no more complications, such as recurrence[57]. ADMs represent a promising option for managing DFUs, offering several benefits that can enhance healing and improve patient outcomes. However, careful consideration of the patient's specific circumstances and

Table 1 Some of the commonly available acellular dermal matrices

ADM	Source	Processor
Alloderm®	Human	LifeCell Corp., Bridgewater, NJ, United States
Allomax®	Human	CR Bard/Davol Inc., Cranston, RI, United States
DermACELL®	Human	LifeNet Health Inc., Virginia Beach, VA, United States
NeoForm®	Human	Mentor, United States
Ethicon®	Human	Ethicon Inc., Somerville, NJ, United States
MatriDerm®	Bovine	Dr Suwelack AG, Billerbeck, Germany
Integra™	Bovine	Life Sciences, Princeton, NJ, United States
Renoskin®	Bovine	Perouse Plastie, France
Permacol™	Porcine	Medtronic, Minneapolis, MN, United States
Strattice®	Porcine	Allergan, Madison, NJ, United States
CollaMend™	Porcine	CR Bard/Davol Inc., Cranston, RI, United States

Table 2 Clinical evidence examples of the utilization of acellular dermal matrix in burn

Ref.	Year	Title	Note
Li *et al*[45]	2015	Human acellular dermal matrix allograft: A randomized, controlled human trial for the long-term evaluation of patients with extensive burns	This randomized controlled clinical trial of human acellular dermal matrix (ADM) showed that the composite graft of human ADM with thinner split-thickness skin graft could provide acceptable esthetic outcomes, good functional recovery, and less scar formation at the donor site
Heimbach *et al*[33]	2003	Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment	Integra® has been found useful in postburn reconstructive procedures both for pediatric and adult patients, affording improved cosmetic results. It clearly provides a valuable, effective and safe clinical treatment modality for dealing with the difficult clinical management challenge posed by the extensively burned patient
Nguyen *et al*[32]	2010	An objective long-term evaluation of Integra (a dermal skin substitute) and split thickness skin grafts, in acute burns and reconstructive surgery	Authors conclude that when objectively measured ADM treated sites correlate well with subject's normal skin elasticity whilst no correlation was seen with the subject's skin grafted sites
Guo *et al* [35]	2016	Use of porcine acellular dermal matrix following early dermabrasion reduces length of stay in extensive deep dermal burns	In this retrospective study authors conclude that early dermabrasion combined with porcine ADM coverage facilitates wound healing, decreases the length of hospital stay, and improves esthetic and functional results in extensive deep dermal burns of adult patients
Wang *et al* [51]	2020	Clinical Applications of Allograft Skin in Burn Care	This compact review summarizes the current use of ADMs and skin allografts in burns in the light of clear evidence
Chen *et al* [47]	2024	Multicenter effect analysis of one-step acellular dermis combined with autologous ultra-thin split thickness skin composite transplantation in treating burn and traumatic wounds	In this open, randomized, controlled, multicenter study, the authors suggest that ADMs can be successfully combined with partial-thickness skin grafts in many other acute traumatic and chronic non-burn wounds

potential challenges is essential for optimal use.

ADMs have also shown efficacy as an adjunct in lower limb venous ulcers treatment. In one of the randomized controlled trial[58], ADM resulted in greater reduction in wound size at 24 weeks (59.6% ADM *vs* 8.1% control). Additionally, all of the ADM-treated wounds remained healed at four weeks postoperatively and 75% remained healed at 12 weeks compared to 66.7% at four weeks and 33.3% at 12 weeks in the control group.

Although their lower quality, there are some studies[59-61] indicating that the ADM can be particularly useful when treating exposed tendons and bones that may be unsuitable for skin graft coverage. Despite their low quality, there are some studies[59-61] showing that ADM may be particularly useful in the treatment of exposed tendons and bones that may not be suitable for skin grafting. According to these studies, ADMs applied after appropriate debridement of exposed bone and tendon segments accelerate granulation in these areas and make the wound bed favorable for grafting.

ADMs have also been associated with complications in chronic wound management, such as hypopigmentation; failure of vascularization, absence of hair follicles, sweat and sebaceous glands; and incomplete innervation[62].

Breast

To date, the increasing rates of breast reconstruction with the effort to achieve the best aesthetic result in less step with minimal complications have made breast surgery the most studied and clinically evidenced area for ADMs. The first ADM-related report in breast surgery was reported by Duncan[63] in 2001 in aesthetic implant surgery. This series, which

Table 3 Clinical evidence examples of the utilization of acellular dermal matrix in various chronic wounds

Ref.	Year	Title	Note
Luthringer *et al*[56]	2020	Human-derived Acellular Dermal Matrix Grafts for Treatment of Diabetic Foot Ulcers: A Systematic Review and Meta-analysis	Authors conclude that Human-derived acellular dermal matrices (ADMs) are associated with a higher likelihood of complete healing and fewer days to complete healing within a 12-week and 16-week periods when compared with standard of care
Gormley *et al* [52]	2024	The use of fetal bovine acellular dermal matrix in severe diabetic foot ulceration and threatened limbs with tissue loss the use of FBADM as an adjunct for complex wounds	Authors conclude that ADM may be a useful adjunct in the acute setting of complex diabetic foot disease and critical limb-threating ischemia ulceration to assist with wound healing
Climov *et al* [53]	2016	The Role of Dermal Matrices in Treating Inflammatory and Diabetic Wounds	Authors review wide range of inflammatory wounds such as pyoderma gangrenosum, sickle cell ulcer, sarcoid ulcer as well as diabetic foot ulcer where ADMs may enhance the regenerative potential
Zelen *et al*[55]	2018	An aseptically processed, acellular, reticular, allogenic human dermis improves healing in diabetic foot ulcers: A prospective, randomised, controlled, multicentre follow-up trial	This randomized controlled trial demonstrates the effectiveness of the human derived ADM in facilitating the closure of nonhealing diabetic foot ulcers refractory to standard of care
Cazzell[58]	2019	A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers	According to this multicenter, randomized, controlled, open-label trial, authors conclude that successful increase in healing rates and rate of percent wound closure in ADM application as compared with conventional care options
Strauss and Brietstein[59]	2012	Fetal Bovine Dermal Repair Scaffold Used for the Treatment of Difficult-to- Heal Complex Wounds	Authors conclude that ADMs can be used as part of an effective treatment regimen to heal complex wounds with exposed tendon/bone caused by varying etiologies

reported the prevention of implant rippling by thickening the tissue envelope, was followed by the successful use of ADMs in aesthetic revisional implant surgeries[64]. Not surprisingly, the use of ADMs then expanded to reconstructive breast surgery[65] and the development of technical properties of ADMs and their clinical utility has accelerated. Presently, ADMs are used routinely in many centers in both primary and revisional alloplastic breast reconstructive and aesthetic surgery. ADMs are generally preferred in one-stage, direct-to-implant surgeries to strengthen the soft tissue envelope in the inferior and lateral breast pole by being sutured between the lower edge of the pectoral muscle and the inframammary fold to reinforce the implant pocket as a sling (Figure 2), while in two-stage breast reconstructions, they are used to strengthen the soft tissue envelope in the inferior and lateral pole of the breast to be expanded and projected. Thus, the surgeon can have greater control and handling over breast projection, lower pole fullness and inframammary fold position. A systematic review of 1039 one-stage immediate breast reconstructions with either ADM showed low overall rates of skin and nipple necrosis (11% and 5%, respectively), infection (12%), hematoma (1%) and seroma (5%), with only 9% of patients requiring reoperation[66]. Also, Nahabedian and Jacobson[67] reported low infection and seroma rates in their multiple series with two-stage reconstruction combined with ADM. In these patients, while the range of surgical site infection was 2.4%-8.1% in prepectoral and 4.8%-11.5% in partial subpectoral reconstructions, seroma was seen in a range of 3.6%-15% in prepectoral and 2.4%-6.5% in partial subpectoral reconstructions. The reconstructive failure rates were also favorable in these patients (subpectoral range 4.3%-15.4%, prepectoral range 1.2%-8.5%). The benefits of ADM in reducing capsular contracture with implants placed in the subpectoral position have been also well documented[68]. Indeed, studies of prepectoral placement of devices without ADM have demonstrated higher rates of capsular contracture[69] compared to when ADM is used. Besides reconstructive era, by inserting ADM prophylactically in primary breast augmentation patients, Hester *et al*[70] reported zero capsular contracture in 49 women.

Placement of implants in the prepectoral plane by wrapping partially or completely with ADM sheets is also a promising and more popular option, and this technique promises greater patient comfort along with better aesthetic results, while reducing pectoral muscle-related morbidities, such as pain, animation deformity and displacement[71-73]. However, although early reports showed that this plane was associated with more complications, more recent reports[74,75] and a meta-analysis[76] indicate similar complication rates when compared to subpectoral plane.

In revision cosmetic surgery, ADMs are used to provide soft tissue reinforcement that is often lacking in augmentation patients, to reinforce breast pockets to correct implant malposition, and to reinforce thinned soft tissue to correct rippling. Furthermore, matrices have also been used in primary mastopexy or reduction mastopexy to provide dermal support to improve breast shape and projection and to prevent "bottoming out"[63,64,70,78]. In addition, ADMs are increasingly securing their position as an important backup player in surgeon's armamentarium in the correction of complications and deformities such as symmastia, capsular contracture and rippling, that may develop after both aesthetic and reconstructive surgeries[78,79]. Table 4 provides examples of current clinical evidence for the use of ADMs in breast surgery.

Despite promising reports, ADM is not without its drawbacks in the breast. Many reports have also shown ADM to result in significantly increased risk of certain complications[80-82] such as seroma, infection, skin necrosis and reconstructive failure. Much of the expertise along with the promising results are usually derived from case series of certain number of surgeons who steadily use ADM. While many results are promising, as in other application fields, the absence or paucity of high-quality, randomized controlled data in regard to ADM use in breast-related surgeries prevents clearly define indications as well as creating algorithms and limits[83] their generalizability and reproducibility.

Table 4 Clinical evidence examples of the utilization of acellular dermal matrix in breast surgery

Ref.	Year	Title	Note
Sigalove *et al* [71]	2017	Prepectoral implant-based breast reconstruction: Rationale, indications, and preliminary results	In this report, the authors discuss the rationale for prepectoral implant reconstruction, its indications/contraindications, and preliminary results from over 350 reconstructions
Chopra *et al* [72]	2021	The Journey of Prepectoral Breast Reconstruction through Time	Authors review the breast reconstruction history and favor prepectoral implant placement. They also encourage the use of acellular dermal matrix (ADM)/Synthetic Mesh with prepectoral breast reconstruction as they are an efficient and effective mode of breast reconstruction, causing minimal morbidity whilst providing good cosmesis
Haddock *et al* [73]	2021	Prepectoral versus Subpectoral Tissue Expander Breast Reconstruction: A Historically Controlled, Propensity Score-Matched Comparison of Perioperative Outcomes	When compared two groups, authors found similar rates of overall perioperative complications. However, prepectoral placement might reduce unnecessary clinic visits; shorten the delay before adjuvant therapy, and minimize patient apprehension, pain, and discomfort related to clinic-based expansion
Nahabedian and Jacobson [67]	2019	Two-stage prepectoral breast reconstruction	Authors suggest that the prepectoral two-stage approach is indicated in the majority of patients and can be performed with fewer complications using ADM, especially in patients who will receive radiotherapy
Asaad *et al*[74]	2023	Surgical and Patient-Reported Outcomes of 694 Two-Stage Prepectoral versus Subpectoral Breast Reconstructions	A large population reconstructed with ADM. Analysis demonstrated overall similar complication rates between the two-implant plane
Sbitany *et al* [75]	2017	A Safe Alternative to Submuscular Prosthetic Reconstruction following Nipple-Sparing Mastectomy	After two-staged implant reconstructions with ADM, analysis revealed no difference in total complication rate between the two groups and no differences in any of the individual complications measured that included infection, seroma and explantation
Nahabedian and Spear[79]	2011	Acellular dermal matrix for secondary procedures following prosthetic breast reconstruction	Authors defines novel ADM involving techniques for correcting deformities and complications, such as rippling, displacement, capsular contracture *etc.*
Kaufman[78]	2012	Pocket reinforcement using acellular dermal matrices in revisionary breast augmentation	Author describes techniques for correcting deformities with ADM after primary breast augmentation

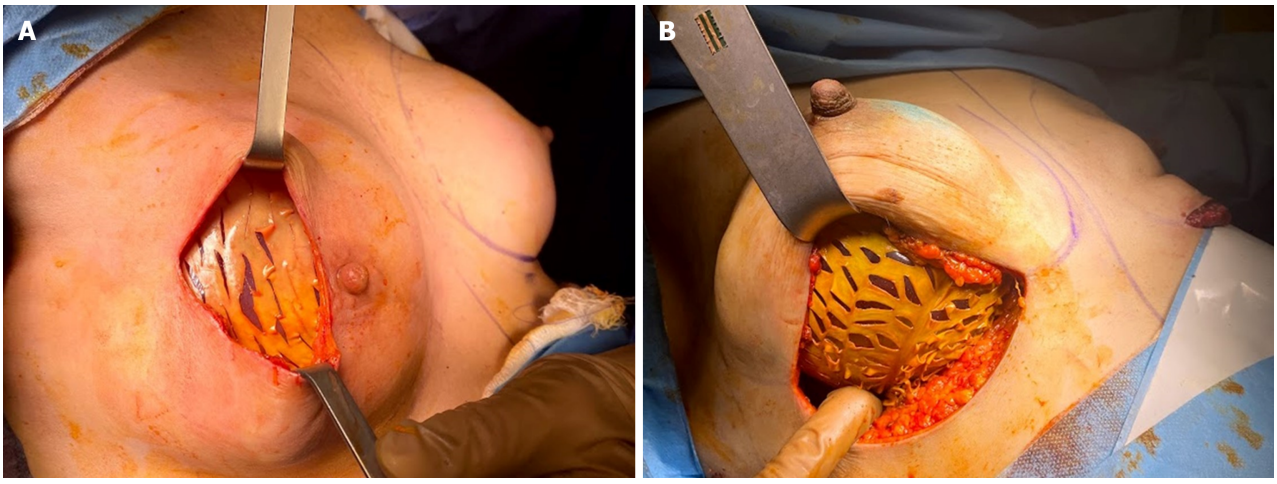

Figure 2 Two case examples for acellular dermal matrix-assisted breast surgery. Left represents breast one stage reconstruction after nipple sparing mastectomy. Right is for a revisional implant exchange and mastopexy. Fenestrated acellular dermal matrix is preferred for both cases.

Although the one of the most studied in the body fields, ADM costs are still another issue of concern in breast. Despite the baseline cost increases some authors found this cost-effective technology in single[24] and two-stage reconstructions [23,24]. In the contrary, in their retrospective comparative study, Viezel-Mathieu *et al*[28] reported 25% less costs in one-stage ADM-sparing technique compared to their traditional two-stage technique using ADM. A randomized controlled trial[26] also showed, despite the similar health status at the end, one-stage reconstruction using ADM is associated with higher costs compared with the traditional two-stage reconstruction. As can be appreciated, the literature does not seem to have reached a consensus on costs. To determine the impact and effectivity of ADMs on the costs of aesthetic breast surgery, large prospective observational studies with more standardized techniques are needed to evaluate outcomes in the long term.

Many questions are yet to be answered regarding ADM in breast surgery, and hopefully the design of high-quality studies will begin to define a clearer data about their use. In this way, the contribution, or advantages of ADMs over

conventional methods can be offered as a more predictable option and the economic cost of the procedure can be undertaken with less risk.

Chest

Most chest wall defects result from oncologic resections and require meticulous reconstructive planning depending on the size and/or location of the defect, the patient's comorbidities and the condition of local tissues. It is also necessary to create a tissue composition that will protect the internal organs and support the upper extremities whilst not complicating the ventilation. Furthermore, a The use of ADMs for chest wall reconstruction was first reported by Cothren *et al*[84] in 2004 and since then, the defined utilities of the ADMs for chest wall reconstruction can be summarized as follows: To support local soft tissue coverage for small thoracic defects, to stabilize the chest wall in large musculoskeletal defects, to correct congenital and acquired contour deformities, and to support the barrier function of autologous flaps in covering the thoracic cavity. In addition, another reason to prefer ADMs for chest wall reconstruction over synthetic materials is that there is a large body of basic science evidence showing that ADMs have increased resistance to infection, and, even in case of infection, treatment can be performed without removal of the material[85]. Although there are no evidence-based guidelines or standardized approaches in terms of the need for ADM use and surgical technique, the literature provides examples of highly successful reconstructions[84-88] (Table 5).

Abdominal wall

Abdominal wall reconstruction remains a complex problem for both plastic and general surgeons. The use of traditional synthetic materials such as polypropylene, polyethylene terephthalate and polytetrafluoroethylene has lost favor to mildly absorbable or partially absorbable materials such as polyglactin or poliglecaprone[89,90]. However, the indications for use or preference for any of these materials are not clear, and none of them is an appropriate choice, especially in contaminated areas. In such defects, where complications such as visceral adhesion, fistula formation, infection, seroma and wound dehiscence are also on the rise, the rate of removal of the meshes can reach 50%-90%[91]. With synthetic meshes failing to meet the needs of the patient in certain circumstances, ADM has become an important consideration in abdominal wall reconstruction of the selected cases. Perhaps the most significant advantage is the opportunity for use in contaminated fields where synthetic meshes are contraindicated (typically, these are Ventral Hernia Working Group class 3 and 4 hernias). Baumann and Butler[89] advocated the first report including such scenarios (grossly contaminated fields, patients have high risk factors for wound healing complications, where increased resistance to infection is desired, direct coverage of viscera and predicted reoperation because of the use of synthetic mesh) which all have been further investigated[92-95] and commonly adopted[96,97] later on. However, well-known risk factors of abdominal wall surgery such as obesity, recurrent hernias, concomitant digestive surgery, smoking and ongoing infection are associated with increased hernia recurrence, and this rate may still remain high in the use of ADM[98,99]. Among complications, reconstructive failure leading recurrence is the most interested and ranges from 6% to as high as 100%[100,101]. The wide range of complications reported in this way has intensified the investigation of the types of ADMs used. Among the ADMs of human, bovine and porcine origin, all of which bear different nuances of use, the high recurrence rates reported in human-derived ADMs[96,97,100,102-105] have greatly increased the interest in animal-derived ADMs. More recently, Lightfoot *et al*[106] performed a well-designed retrospective cohort study comparing 40 consecutive patients who underwent open component separation with porcine ADM reinforcement to 39 consecutive patients who underwent open component separation with bovine ADM. They reported that bovine ADM was statistically significantly superior in terms of wound complications, while recurrence and reasons requiring reoperation were less common but not statistically significant. This indicates that even with the diverse array of xenogeneic meshes on the market, the ideal mesh is yet to be identified. While the chosen ADM product certainly contributes to the failure, there is ample data to suggest that this extremely wide failure range is not solely due to the chosen product. For example, Garvey *et al*[104] in their high-volume single center study not only reported remarkable recurrence rates of 11.5% and 14.6% detected by CT at 3 and 5 years, respectively, but also demonstrated that bridged repair technique was highly unsuccessful in preventing recurrence compared to primary fascial repair technique and reinforcement with ADM. Indeed, in addition to superiority of xenogeneic ADM, there are two more points that literature agrees upon. First, primary fascial repair with the use of ADM as reinforcement has repeatedly been shown to be superior to bridged repair technique in preventing recurrence[101-105] and second, component separation technique facilitates fascial closure and reduces overall complications when used in conjunction with ADM[105-108]. Even though there are descriptions for different surgical variables commonly used, such as suture choice, fascial overlap amount and suture technique for ADM, lack of standardization in these data warrants further studies. As with other ADM applications, paucity of randomized controlled studies with long-term outcomes limits the opportunity to draw more specific therapeutic conclusions about ADM in abdominal wall repair. Table 6 summarizes the some of the clinical evidence for ADM use in abdominal wall repair.

Head and neck

Besides the oral-maxillofacial, head and neck and craniofacial reconstructive procedures, there is an increasing number of evidence that ADMs can be used for aesthetic purposes. In 2012, Shridharani and Tufaro[109] compiled a systematic review of nearly 3 dozen studies with objective and measurable results, including surgeries such as nasal soft tissue and skeletal repair[110,111], tympanoplasty[112], parotidectomy sequelae[113,114], oral-mucosal[115], palatal[116] and pharyngeal defects[117] and fistulas as well as periorbital soft tissue[118] and dura mater[119] reconstructions. Today, however this number has probably reached several hundred, making the head and neck as a whole the most comprehensive area for the use of ADM. There was an inspiring earlier report of Clark *et al*[120], which consisted of 7 consecutive patients with clefts of the hard and soft palate wider than 15 mm. Palates were repaired in the standard 2-flap approach

Table 5 Clinical evidence examples of the utilization of acellular dermal matrix in chest wall reconstruction

Ref.	Year	Title	Note
Sodha *et al* [85]	2012	The use of acellular dermal matrices in chest wall reconstruction	First review of acellular dermal matrix (ADM) utilization in chest wall defects. Authors share their experiences and conclude that they favor acellular dermal matrices when there is concern for possible field contamination, active infection, or concern over wound healing
Cothren *et al* [84]	2004	Chest wall reconstruction with acellular dermal matrix (AlloDerm) and a latissimus muscle flap	First case report utilizing ADM in a chest wall defect
Khalil *et al* [86]	2018	Chest Wall Reconstruction with Porcine Acellular Dermal Matrix (Strattice) and Autologous Tissue Transfer for High Risk Patients with Chest Wall Tumors	Reconstruction 7 sarcoma and 1 breast cancer resection involving chest wall. Authors encourage ADM use in chest wall reconstruction to resist infection in high-risk patients with extensive defects
Alshehri[87]	2023	Chest wall osteochondroma resection with biologic acellular bovine dermal mesh reconstruction in pediatric hereditary multiple exostoses: A case report and review of literature	Resection and ADM involving reconstruction of a 5-year-old
Delgado-Miguel *et al* [88]	2022	The Use of Acellular Dermal Matrix (Integra Single Layer) for the Correction of Malformative Chest Wall Deformities: First Case Series Reported	Four cases of congenital chest malformation

Table 6 Clinical evidence examples of the utilization of acellular dermal matrix in abdominal wall reconstruction

Ref.	Year	Title	Note
Zhong *et al* [96]	2011	Outcomes after abdominal wall reconstruction using acellular dermal matrix: a systematic review	Authors conclude the need for high-level evidence when comparing acellular dermal matrix (ADM) use with other methods to make data-driven recommendations on clinical indications, surgical techniques and outcomes following ADM-assisted abdominal wall reconstruction
Sbitany *et al*[98]	2015	Outcomes Analysis of Biologic Mesh Use for Abdominal Wall Reconstruction in Clean-Contaminated and Contaminated Ventral Hernia Repair	Authors conclude that single-stage repair of grade 3 hernias performed with component separation and biologic mesh reinforcement is effective and offers a low recurrence rate. The use of biologic mesh allows for avoidance of mesh explantation in instances of wound breakdown or infection. Bridging repairs are associated with a high recurrence rate, as is single-stage repair of grade 4 hernias
Atema *et al* [99]	2017	Major Complex Abdominal Wall Repair in Contaminated Fields with Use of a Non-cross-linked Biologic Mesh: A Dual-Institutional Experience	Author proposes that the repair of the most challenging abdominal wall defect can be done effectively with combination of a non-cross-linked biologic mesh and component separation technique without the need for mesh removal despite wound infections
Hassan *et al*[107]	2023	Outcomes of Complex Abdominal Wall Reconstruction After Oncologic Resection: 14-Year Experience at an NCI-Designated Cancer Center	Authors conclude that ADM-assisted abdominal wall repair after extirpative wall resections demonstrated comparable outcomes with primary herniorrhaphy
Giordano *et al*[108]	2024	Component Separation Decreases Hernia Recurrence Rates in Abdominal Wall Reconstruction with Biologic Mesh	Authors concluded that the component separation technique combined with ADM was associated with fewer hernia recurrences, while surgical site occurrence was similar in long-term follow-up despite additional surgery

with intravelar veloplasty and placement of ADM immediately deep to the oral mucosal closure. There were no fistulas even though the wound dehiscence and ADM exposure occurred in two patients in early period. Since then, a growing body of evidence suggests that ADM is an effective adjunct in the repair of cleft[121,122]. More recently, some authors, based on their prospective studies, also recommend the routine use of ADM in primary palate repair due to reduced fistula rates[116]. Some meta-analyses advocate the routine use of ADM after parotidectomy[114], citing the lower incidence of Frey syndrome since its constitution as an extra durable anatomic layer between remaining parotid and dermis. One meta-analysis also validate that ADM might be an effective alternative to autologous grafts for tympanoplasty[112]. ADMs can be used internally to repair nasal septal perforations by placing as a graft between mucoperichondrial flaps and therefore it can increase the durability of the repair where watertight closure is essential[123,124]. ADMs are also still a particularly valuable tool in the treatment for patients with mucosal defects of the oral cavity (tongue, floor of mouth, palate, lip, and tonsil) following resection of primary intraoral tumors and they can provide an alternative to split-thickness skin grafting for mucosal resurfacing[115]. In addition to reconstructive procedures, it worths to mention that the use of ADMs in aesthetic-related procedures has become more widespread. ADM, for instance, has established itself as an important tool in blepharoplasty-related procedures such as correction of lower eyelid retraction[125,126] and restoring orbital septal tone[118]. In primary and revisional secondary rhinoplasty surgeries, ADM can be useful when correcting dorsal nasal irregularities[110,111] and osseocartilaginous frame[127] by on lay grafting ADM at the expense of prolonged edema. These examples may be interpreted as the utility of ADM in the head and neck region have started to consolidate with higher quality clinical evidence although more high-quality studies in all examples are still warranted to make evidence-based recommendations. Table 7 lists some of the important clinical

Table 7 Clinical evidence examples of the utilization of acellular dermal matrix in head and neck

Ref.	Year	Title	Note
Shridharani and Tufaro [109]	2012	A systematic review of acelluar dermal matrices in head and neck reconstruction	First systematic review for the head and neck region
Gilardino *et al* [116]	2018	A Prospective Study Investigating Fistula Rate Following Primary Palatoplasty Using Acellular Dermal Matrix	This prospective study proposes the routine use of ADM in Veau II-IV clefts since it significantly reduce the fistula rate when compared their retrospective cohort
Linn *et al*[114]	2022	Comparison of the use of allogenic acellular dermal matrix on rates of Frey syndrome post parotidectomy: A systematic review and meta-analysis	Authors conclude that the use of ADM was associated with lower Frey syndrome rates compared to no ADM and should be considered in routine use to prevent this condition
Xu *et al*[112]	2021	Human-derived acellular dermal matrix may be an alternative to autologous grafts in tympanic membrane reconstruction: systematic review and meta-analysis	Authors conclude that human-derived ADM might be an effective alternative to autologous grafts for tympanoplasty
Girod *et al* [115]	2009	Acellular dermis compared to skin grafts in oral cavity reconstruction	Authors conclude that acellular dermis grafting for reconstruction of the oral cavity offers several advantages over split-thickness skin graft, including the lack of donor site morbidity, lower cost, a natural appearing mucosal surface, and comparable if not superior functional status
Warren *et al* [119]	2000	Dural repair using acellular human dermis: experience with 200 cases: technique assessment	Authors conclude that acellular human dermis is a reasonable alternative to the available dural graft materials. Its handling characteristics are similar to those of dura, it is biologically inert, and it does not produce adhesion formation
Zang *et al*[117]	2020	Comparison of xenogeneic acellular dermal matrix and skin grafts in reconstruction of postoperative defects of hypopharyngeal cancer: A retrospective cohort study	Authors conclude that both ADM and abdominal skin grafts demonstrated good effects in the reconstruction of hypopharynx, but the recovery time of eating function in patients with ADM was faster, which may be due to rapid epithelialization
Conrad *et al* [124]	2018	Acellular Human Dermal Allograft as a Graft for Nasal Septal Perforation Reconstruction	Authors conclude that as the first study to use objective and subjective measurements to confirm success with acellular dermis allograft as an adjunct for septal perforation repair it demonstrated a statistically significant reduction in patient nasal symptoms following repair
Grumbine *et al* [126]	2019	Correction of Lower Eyelid Retraction with En Glove Placement of Porcine Dermal Collagen Matrix Implant	Authors describe the technique for mild to moderate retractions. The operative time is brief (< 30 minutes), with limited dissection and resultant minimal to no clinically significant ocular surface inflammation postoperatively
Kook *et al*[110]	2023	Prevention and Resolution of Silicone Implant-Related Problems in Secondary Rhinoplasty Using a Cross-Linked Human Acellular Dermal Matrix	Authors conclude that dorsal augmentation using the cross-linked human ADM along with various nasal tip work using autogenous cartilage. Surgical outcome showed favorable resolution of contracture deformities, a low infection rate, firm fixation of the implant, good skin texture/thickness of the skin/soft tissue envelope and gain of desired height and dorsal line
Fisher *et al* [111]	2023	Current Practices in Dorsal Augmentation Rhinoplasty	Authors describe acellular dermal matrices are alternatives to autologous graft with many similar advantages and no need for an additional surgical site

evidence examples of ADM utility in head and neck region.

Extremity

The use of ADMs in the extremities is widespread and varied, with burns, contractures and scars constituting the majority. The frequency of injuries, especially in the distal upper extremity, the scarcity of local soft tissues and the abundance of superficial nerves and vessels make this region the center of many up-to-date applications. However, the majority of the clinical evidence in this region are mostly either limited studies or small case series. However, some of the important, noteworthy uses in some fields are also listed in Table 8.

In both primary and revision rotator cuff repairs, some studies reported incorporation of ADMs has led to improvements in pain, ROM and muscle strength in long-term follow-ups[128,129]. Furthermore, in irreparable rotator cuff tears, ADMs have been used to cover the exposed bone, leading to decreased pain and better functional scores[130]. Efforts to reinforce or augment the deficient long tendon repairs have led combining them with ADMs. Cole *et al*[131] successfully repaired 9 Achilles tendon with ADM augmentation without any complications requiring re-operation. Postoperative flexor tendon adhesion in hand is annoying and it can contribute to functional disability and reconstructive failure. In their prospective study Shim *et al*[132] found improved ROM and function in ADM-treated group at six months. Arthritic hands have also long been difficult cases. Reconstruction of ligaments or resurfacing damaged joints usually requires donor tendon, but this might often associate with scarring, chronic pain, tendonitis, and rupture. Using ADM rather own tissue may significantly reduce the donor site related morbidity[133,134]. While there are some studies investigating and showing benefit of the use of ADM for other upper extremity applications, such as Dupuytren disease [135], congenital malformations, and traumatic reconstructions[37] these are limited studies or small case series. As in the other uses in extremities further investigation into these proposed uses is also warranted.

Table 8 Clinical evidence examples of the utilization of acellular dermal matrix in extremity

Ref.	Year	Title	Note
Acevedo *et al* [128]	2015	Orthopedic applications of acellular human dermal allograft for shoulder and elbow surgery	Authors review a wide variety of orthopedical applications of acellular dermal matrices (ADMs) such as, rotator cuff tears, latissimus dorsi transfers, pectoralis major and biceps tendon repairs, glenoid resurfacing and acromioclavicular reconstruction
Cole *et al*[131]	2018	Achilles Tendon Augmented Repair Using Human Acellular Dermal Matrix: A Case Series	Authors report no cases of rerupture or complications that require additional treatment over average of 14.4 months of nine patient
Rabinovich and Lee[134]	2018	Proximal Row Carpectomy Using Decellularized Dermal Allograft	Authors describe their ADM-assisted resurfacing technique with illustration and figures
Hoang *et al* [135]	2019	Use of Acellular Dermal Matrix Following Fasciectomy for the Treatment of Dupuytren's Disease	Authors conclude that the adjunct placement of acellular dermal matrix into the wound bed following fasciectomy may be an important surgical strategy to reduce recurrence rates as well as augment coverage of exposed vital structures in cases of severe flexion contracture
Ellis and Kulber[37]	2012	Acellular dermal matrices in hand reconstruction	A comprehensive review for ADM-assisted reconstruction of difficult skin and soft tissue defects resulted from various etiologies such as, ischemia, infection, advanced Dupuytren disease and burn contractures
Shim *et al*[132]	2021	Preventing postoperative adhesions after hand tendon repair using acellular dermal matrix	Authors conclude that he use of ADM after tendon repair has the potential to significantly improve the outcome of tendon surgery in terms of range of motion

CONCLUSION

After the processing journey of ADMs, which starts as allo- or xeno-product, the market generously offers them to us in a package like synthetic merchandise, and after the appropriate implantation technique, they adapt the body as if they were already part of it, without any alienation. This review demonstrated that as manufacturing technology improved and their popularity grew, ADMs found their way into the surgeon's armamentarium for a wide range of conditions. The compelling clinical examples showcased in this study affirm that the applications of human ADM extend significantly beyond its initial use for skin defect treatments. Although the literature is encouraging in almost all areas, more rigorous and higher-quality prospective studies are needed for more widespread use. It is clear that these products, which tissue engineering and bioengineering have already made practical and widely available, will be further developed in the future.

Experimental studies are ongoing with the aim of evolving ADM-based scaffolds into the desired 3D shape[136], combining them with stem cells[137] and growth factors[138]. Although many of these ideas are still in the proof-of-concept phase, there are also exciting clinical applications with some early promising results in patient trials[53,139-140].

Another development that has become very important in the recent past is synthetic substitutes or templates. Known as, biodegradable temporizing matrix (BTM), this completely synthetic bilayer skin substitute is made of a biodegradable polyurethane matrix foam covered with a nonbiodegradable polyurethane sealing membrane to mimic the dermis and epidermis, respectively[141]. When placed over a wound, it promotes vascularization and dermal regeneration[142]. Polyurethane was selected for its low manufacturing cost and ability to withstand infection, combating two important limitations of biological dermal scaffolds[143]. Although BTM has shown promising results as a lower-cost skin substitute in preliminary reports, it is also carrying out very exciting and successful missions in the use of skin as a highly vascularized bed for transplantation of islet cells[144] or as a scaffold for adrenal organoid formation in adrenocortical cell transplantations[145]. Indeed, it would not be surprising to see an increase in successful cell transplantations using BTM in the next decade. Until all the rapidly developing processes of whole organ decellularization and recellularization have been perfected, ADM and BTM will likely maintain their potential as a reliable scaffold for many cells to adapt and proliferate.

FOOTNOTES

Author contributions: Dilek ÖF, Sevim KZ, and Dilek ON contributed to this paper; Dilek ÖF designed the overall concept and outline of the manuscript; Sevim KZ contributed to the literature review and design of the manuscript; Dilek ÖF and Sevim KZ contributed to the writing, and editing the manuscript, table, and references; Dilek ON made supervision and final proofing in all aspects.

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

Country of origin: Türkiye

ORCID number: Ömer F Dilek 0000-0001-9650-3806; Kamuran Z Sevim 0000-0002-9625-6670; Osman N Dilek 0000-0002-6313-3818.

S-Editor: Gao CC
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Nelson CM**, Bissell MJ. Of extracellular matrix, scaffolds, and signaling: tissue architecture regulates development, homeostasis, and cancer. *Annu Rev Cell Dev Biol* 2006; **22**: 287-309 [PMID: 16824016 DOI: 10.1146/annurev.cellbio.22.010305.104315]
2 **Mast BA**, Schultz GS. Interactions of cytokines, growth factors, and proteases in acute and chronic wounds. *Wound Repair Regen* 1996; **4**: 411-420 [PMID: 17309691 DOI: 10.1046/j.1524-475X.1996.40404.x]
3 **Janis JE**, Nahabedian MY. Acellular dermal matrices in surgery. *Plast Reconstr Surg* 2012; **130**: 7S-8S [PMID: 23096990 DOI: 10.1097/PRS.0b013e31825f2d20]
4 **Banyard DA**, Bourgeois JM, Widgerow AD, Evans GRD. Regenerative biomaterials: a review. *Plast Reconstr Surg* 2015; **135**: 1740-1748 [PMID: 26017603 DOI: 10.1097/PRS.0000000000001272]
5 **Tenenhaus M**, Rennekampff HO. Current Concepts in Tissue Engineering: Skin and Wound. *Plast Reconstr Surg* 2016; **138**: 42S-50S [PMID: 27556774 DOI: 10.1097/PRS.0000000000002685]
6 **Boháč M**, Danišovič Ľ, Koller J, Dragúňová J, Varga I. What happens to an acellular dermal matrix after implantation in the human body? A histological and electron microscopic study. *Eur J Histochem* 2018; **62**: 2873 [PMID: 29569868 DOI: 10.4081/ejh.2018.2873]
7 **DeGeorge BR Jr**, Ning B, Salopek LS, Pineros-Fernandez A, Rodeheaver GT, Peirce-Cottler S, Hu S, Cottler PS, Campbell CA. Advanced Imaging Techniques for Investigation of Acellular Dermal Matrix Biointegration. *Plast Reconstr Surg* 2017; **139**: 395-405 [PMID: 28121875 DOI: 10.1097/PRS.0000000000002992]
8 **Lee JH**, Kim HG, Lee WJ. Characterization and tissue incorporation of cross-linked human acellular dermal matrix. *Biomaterials* 2015; **44**: 195-205 [PMID: 25617138 DOI: 10.1016/j.biomaterials.2014.12.004]
9 **Crapo PM**, Gilbert TW, Badylak SF. An overview of tissue and whole organ decellularization processes. *Biomaterials* 2011; **32**: 3233-3243 [PMID: 21296410 DOI: 10.1016/j.biomaterials.2011.01.057]
10 **Keane TJ**, Swinehart IT, Badylak SF. Methods of tissue decellularization used for preparation of biologic scaffolds and in vivo relevance. *Methods* 2015; **84**: 25-34 [PMID: 25791470 DOI: 10.1016/j.ymeth.2015.03.005]
11 **Gilpin A**, Yang Y. Decellularization Strategies for Regenerative Medicine: From Processing Techniques to Applications. *Biomed Res Int* 2017; **2017**: 9831534 [PMID: 28540307 DOI: 10.1155/2017/9831534]
12 **Petrie K**, Cox CT, Becker BC, MacKay BJ. Clinical applications of acellular dermal matrices: A review. *Scars Burn Heal* 2022; **8**: 20595131211038313 [PMID: 35083065 DOI: 10.1177/20595131211038313]
13 **Capella-Monsonís H**, Zeugolis DI. Decellularized xenografts in regenerative medicine: From processing to clinical application. *Xenotransplantation* 2021; **28**: e12683 [PMID: 33709410 DOI: 10.1111/xen.12683]
14 **Brown BN**, Badylak SF. Extracellular matrix as an inductive scaffold for functional tissue reconstruction. *Transl Res* 2014; **163**: 268-285 [PMID: 24291155 DOI: 10.1016/j.trsl.2013.11.003]
15 **Łabuś W**, Kawecki M, Glik J, Maj M, Kitala D, Misiuga M, Klama-Baryła A, Kraut M, Nowak M. Own Experience From The Use Of A Substitute Of An Allogeneic Acellular Dermal Matrix Revitalized With In Vitro Cultured Skin Cells In Clinical Practice. *Pol Przegl Chir* 2015; **87**: 513-521 [PMID: 26812752 DOI: 10.1515/pjs-2015-0097]
16 **Vorotnikova E**, McIntosh D, Dewilde A, Zhang J, Reing JE, Zhang L, Cordero K, Bedelbaeva K, Gourevitch D, Heber-Katz E, Badylak SF, Braunhut SJ. Extracellular matrix-derived products modulate endothelial and progenitor cell migration and proliferation in vitro and stimulate regenerative healing in vivo. *Matrix Biol* 2010; **29**: 690-700 [PMID: 20797438 DOI: 10.1016/j.matbio.2010.08.007]
17 **Barkan D**, Green JE, Chambers AF. Extracellular matrix: a gatekeeper in the transition from dormancy to metastatic growth. *Eur J Cancer* 2010; **46**: 1181-1188 [PMID: 20304630 DOI: 10.1016/j.ejca.2010.02.027]
18 **Minerva F**. New threats to academic freedom. *Bioethics* 2014; **28**: 157-162 [PMID: 24602125 DOI: 10.1111/bioe.12066]
19 **Pontifical Academy for Life**; Working Group, The Holy See, Vatican City. Prospects for xenotransplantation: scientific aspects and ethical considerations. *Natl Cathol Bioeth Q* 2002; **2**: 481-505 [PMID: 12854603]
20 **Teichman J**, Glick S. Jewish Medical Ethics and Xenotransplantation: Challenges and Opportunities. *Harefuah* 2011; **150**: 802-805
21 **Wilks S**. The Ethical Implications of Xenotransplantation. *J Medical Ethics* 2017; **43**: 233-237
22 **Macadam SA**, Lennox PA. Acellular dermal matrices: economic considerations in reconstructive and aesthetic breast surgery. *Clin Plast Surg* 2012; **39**: 187-216 [PMID: 22482360 DOI: 10.1016/j.cps.2012.02.007]
23 **Krishnan NM**, Chatterjee A, Rosenkranz KM, Powell SG, Nigriny JF, Vidal DC. The cost effectiveness of acellular dermal matrix in expander-implant immediate breast reconstruction. *J Plast Reconstr Aesthet Surg* 2014; **67**: 468-476 [PMID: 24508194 DOI: 10.1016/j.bjps.2013.12.035]
24 **Aliotta RE**, Duraes EFR, Scomacao I, Morisada M, Orra S, Moreira A, Bernard S, Schwarz G, Djohan R. A controlled cost and outcomes analysis of acellular dermal matrix and implant-based reconstruction. *J Plast Reconstr Aesthet Surg* 2021; **74**: 1229-1238 [PMID: 33526361 DOI: 10.1016/j.bjps.2020.10.079]
25 **Ávila León JL**, Rivero CR, Guerrero Serrano L, Alviar JD, Rodríguez MA, Arocha AM, Pineda GG. Immediate Results of the Use of Split-Thickness Skin Autografts With and Without Acellular Dermal Matrix in Patients with Burns: A Comparative Study in a Colombian Population. *J Burn Care Res* 2024; **45**: 348-355 [PMID: 37668065 DOI: 10.1093/jbcr/irad131]
26 **Negenborn VL**, Smit JM, Dikmans REG, Winters HAH, Twisk JWR, Ruhé PQ, Mureau MAM, Tuinder S, Eltahir Y, Posch NAS, van Steveninck-Barends JM, van der Hulst RRWJ, Ritt MJPF, Bouman MB, Mullender MG. Short-term cost-effectiveness of one-stage implant-based breast reconstruction with an acellular dermal matrix versus two-stage expander-implant reconstruction from a multicentre randomized clinical trial. *Br J Surg* 2019; **106**: 586-595 [PMID: 30835827 DOI: 10.1002/bjs.11102]

27 **Fischer JP**, Basta MN, Krishnan NM, Wink JD, Kovach SJ. A Cost-Utility Assessment of Mesh Selection in Clean-Contaminated Ventral Hernia Repair. *Plast Reconstr Surg* 2016; **137**: 647-659 [PMID: 26818303 DOI: 10.1097/01.prs.0000475775.44891.56]

28 **Viezel-Mathieu A**, Alnaif N, Aljerian A, Safran T, Brabant G, Boileau JF, Dionisopoulos T. Acellular Dermal Matrix-sparing Direct-to-implant Prepectoral Breast Reconstruction: A Comparative Study Including Cost Analysis. *Ann Plast Surg* 2020; **84**: 139-143 [PMID: 31335468 DOI: 10.1097/SAP.0000000000001997]

29 **Hirpara MM**, Clark RC, Hogan E, Dean R, Reid CM. Rise of Acellular Dermal Matrix: Cost Consciousness, Industry Payment, and Publication Productivity. *J Am Coll Surg* 2023; **236**: 1189-1197 [PMID: 36757115 DOI: 10.1097/XCS.0000000000000648]

30 **Heimbach D**, Luterman A, Burke J, Cram A, Herndon D, Hunt J, Jordan M, McManus W, Solem L, Warden G. Artificial dermis for major burns. A multi-center randomized clinical trial. *Ann Surg* 1988; **208**: 313-320 [PMID: 3048216 DOI: 10.1097/00000658-198809000-00008]

31 **Wainwright DJ**. Use of an acellular allograft dermal matrix (AlloDerm) in the management of full-thickness burns. *Burns* 1995; **21**: 243-248 [PMID: 7662122 DOI: 10.1016/0305-4179(95)93866-i]

32 **Nguyen DQ**, Potokar TS, Price P. An objective long-term evaluation of Integra (a dermal skin substitute) and split thickness skin grafts, in acute burns and reconstructive surgery. *Burns* 2010; **36**: 23-28 [PMID: 19864070 DOI: 10.1016/j.burns.2009.07.011]

33 **Heimbach DM**, Warden GD, Luterman A, Jordan MH, Ozobia N, Ryan CM, Voigt DW, Hickerson WL, Saffle JR, DeClement FA, Sheridan RL, Dimick AR. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil* 2003; **24**: 42-48 [PMID: 12543990 DOI: 10.1097/00004630-200301000-00009]

34 **Sheridan R**, Hegarty M, Tompkins R, Burke J. Artificial skin in massive burns ? results to ten years. *Eur J Plast Surg* 1994; **17** [DOI: 10.1007/bf00176923]

35 **Guo ZQ**, Qiu L, Gao Y, Li JH, Zhang XH, Yang XL, Peszel A, Chen XL. Use of porcine acellular dermal matrix following early dermabrasion reduces length of stay in extensive deep dermal burns. *Burns* 2016; **42**: 598-604 [PMID: 26777449 DOI: 10.1016/j.burns.2015.10.018]

36 **Zhang X**, Deng Z, Wang H, Yang Z, Guo W, Li Y, Ma D, Yu C, Zhang Y, Jin Y. Expansion and delivery of human fibroblasts on micronized acellular dermal matrix for skin regeneration. *Biomaterials* 2009; **30**: 2666-2674 [PMID: 19171377 DOI: 10.1016/j.biomaterials.2009.01.018]

37 **Ellis CV**, Kulber DA. Acellular dermal matrices in hand reconstruction. *Plast Reconstr Surg* 2012; **130**: 256S-269S [PMID: 23096981 DOI: 10.1097/PRS.0b013e318265a5cf]

38 **Askari M**, Cohen MJ, Grossman PH, Kulber DA. The use of acellular dermal matrix in release of burn contracture scars in the hand. *Plast Reconstr Surg* 2011; **127**: 1593-1599 [PMID: 21460666 DOI: 10.1097/PRS.0b013e31820a6511]

39 **Yim H**, Cho YS, Seo CH, Lee BC, Ko JH, Kim D, Hur J, Chun W, Kim JH. The use of AlloDerm on major burn patients: AlloDerm prevents post-burn joint contracture. *Burns* 2010; **36**: 322-328 [PMID: 20080353 DOI: 10.1016/j.burns.2009.10.018]

40 **Pan Y**, Liang Z, Yuan S, Xu J, Wang J, Chen S. A long-term follow-up study of acellular dermal matrix with thin autograft in burns patients. *Ann Plast Surg* 2011; **67**: 346-351 [PMID: 21467908 DOI: 10.1097/SAP.0b013e3182111088]

41 **Bloemen MCT**, van Leeuwen MCE, van Vucht NE, van Zuijlen PPM, Middelkoop E. Dermal substitution in acute burns and reconstructive surgery: a 12-year follow-up. *Plast Reconstr Surg* 2010; **125**: 1450-1459 [PMID: 20440164 DOI: 10.1097/PRS.0b013e3181d62b08]

42 **Haslik W**, Kamolz LP, Manna F, Hladik M, Rath T, Frey M. Management of full-thickness skin defects in the hand and wrist region: first long-term experiences with the dermal matrix Matriderm. *J Plast Reconstr Aesthet Surg* 2010; **63**: 360-364 [PMID: 19042169 DOI: 10.1016/j.bjps.2008.09.026]

43 **Pirayesh A**, Hoeksema H, Richters C, Verbelen J, Monstrey S. Glyaderm(®) dermal substitute: clinical application and long-term results in 55 patients. *Burns* 2015; **41**: 132-144 [PMID: 24946965 DOI: 10.1016/j.burns.2014.05.013]

44 **Nicoletti G**, Brenta F, Bleve M, Pellegatta T, Malovini A, Faga A, Perugini P. Long-term in vivo assessment of bioengineered skin substitutes: a clinical study. *J Tissue Eng Regen Med* 2015; **9**: 460-468 [PMID: 24962375 DOI: 10.1002/term.1939]

45 **Li X**, Meng X, Wang X, Li Y, Li W, Lv X, Xu X, Lei Z, Li J. Human acellular dermal matrix allograft: A randomized, controlled human trial for the long-term evaluation of patients with extensive burns. *Burns* 2015; **41**: 689-699 [PMID: 25687834 DOI: 10.1016/j.burns.2014.12.007]

46 **Shang F**, Hou Q. Effects of allogenic acellular dermal matrix combined with autologous razor-thin graft on hand appearance and function of patients with extensive burn combined with deep hand burn. *Int Wound J* 2021; **18**: 279-286 [PMID: 33547855 DOI: 10.1111/iwj.13532]

47 **Chen L**, Yang J, Wang DY, Jiang JM, Zhang BD, Zhao ZJ, Chen XL, Lv DL. Multicenter effect analysis of one-step acellular dermis combined with autologous ultra-thin split thickness skin composite transplantation in treating burn and traumatic wounds. *Int Wound J* 2024; **21**: e14341 [PMID: 37548136 DOI: 10.1111/iwj.14341]

48 **Almeida IR**, Gonqalves AC, Corrêa FB, Castro JCD, Guirro ECO, Farina JA Junior, Coltro PS. Evaluation of Clinical and Biomechanical Features of Scars Resulting from the Treatment of Burn Contractures Comparing Acellular Dermal Matrices: A Randomized Clinical Trial. *Ann Surg* 2023; **277**: 198-205 [PMID: 35081576 DOI: 10.1097/SLA.0000000000005371]

49 **Corrêa FB**, Castro JCD, Almeida IR, Farina-Junior JA, Coltro PS. Evaluation of contraction of the split-thickness skin graft using three dermal matrices in the treatment of burn contractures: A randomised clinical trial. *Wound Repair Regen* 2022; **30**: 222-231 [PMID: 35141977 DOI: 10.1111/wrr.13002]

50 **Gardien KLM**, Pijpe A, Brouwer KM, Stoop M, Singh SK, Timmermans FW, Vlig M, van Zuijlen PPM, Middelkoop E. Short- and Long-term Outcomes of an Acellular Dermal Substitute versus Standard of Care in Burns and Reconstructions: A Phase I/II Intrapatient Randomized Controlled Trial. *Adv Skin Wound Care* 2023; **36**: 540-548 [PMID: 37729164 DOI: 10.1097/ASW.0000000000000040]

51 **Wang C**, Zhang F, Lineaweaver WC. Clinical Applications of Allograft Skin in Burn Care. *Ann Plast Surg* 2020; **84**: S158-S160 [PMID: 32028339 DOI: 10.1097/SAP.0000000000002282]

52 **Gormley S**, Hart O, French S, O'Shea C, Khashram M. The use of fetal bovine acellular dermal matrix in severe diabetic foot ulceration and threatened limbs with tissue loss the use of FBADM as an adjunct for complex wounds. *Vascular* 2024; **32**: 619-625 [PMID: 36415107 DOI: 10.1177/17085381221141115]

53 **Climov M**, Bayer LR, Moscoso AV, Matsumine H, Orgill DP. The Role of Dermal Matrices in Treating Inflammatory and Diabetic Wounds. *Plast Reconstr Surg* 2016; **138**: 148S-157S [PMID: 27556755 DOI: 10.1097/PRS.0000000000002652]

54 **Hu Z**, Zhu J, Cao X, Chen C, Li S, Guo D, Zhang J, Liu P, Shi F, Tang B. Composite Skin Grafting with Human Acellular Dermal Matrix Scaffold for Treatment of Diabetic Foot Ulcers: A Randomized Controlled Trial. *J Am Coll Surg* 2016; **222**: 1171-1179 [PMID: 27068845 DOI: 10.1016/j.jamcollsurg.2016.02.023]

55 **Zelen CM**, Orgill DP, Serena TE, Galiano RE, Carter MJ, DiDomenico LA, Keller J, Kaufman JP, Li WW. An aseptically processed, acellular, reticular, allogenic human dermis improves healing in diabetic foot ulcers: A prospective, randomised, controlled, multicentre follow-up trial. *Int Wound J* 2018; **15**: 731-739 [PMID: 29682897 DOI: 10.1111/iwj.12920]

56 **Luthringer M**, Mukherjee T, Arguello-Angarita M, Granick MS, Alvarez OM. Human-derived Acellular Dermal Matrix Grafts for Treatment of Diabetic Foot Ulcers: A Systematic Review and Meta-analysis. *Wounds* 2020; **32**: 57-65 [PMID: 32155123]

57 **Lingyan L**, Han Z, Jialu L, Bingyang H, Yuanyuan M, Peiwei Q, Peifen M, Liwei X. Acellular Dermal Matrix for Treatment of Diabetic Foot Ulcer: An Overview of Systematic Reviews. *Int J Low Extrem Wounds* 2023; 15347346231201696 [PMID: 38018121 DOI: 10.1177/15347346231201696]

58 **Cazzell S**. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers. *Wounds* 2019; **31**: 68-74 [PMID: 30720443]

59 **Strauss NH**, Brietstein RJ. Fetal Bovine Dermal Repair Scaffold Used for the Treatment of Difficult-to- Heal Complex Wounds. *Wounds* 2012; **24**: 327-334 [PMID: 25876169]

60 **Rehim SA**, Singhal M, Chung KC. Dermal skin substitutes for upper limb reconstruction: current status, indications, and contraindications. *Hand Clin* 2014; **30**: 239-252, vii [PMID: 24731613 DOI: 10.1016/j.hcl.2014.02.001]

61 **Helgeson MD**, Potter BK, Evans KN, Shawen SB. Bioartificial dermal substitute: a preliminary report on its use for the management of complex combat-related soft tissue wounds. *J Orthop Trauma* 2007; **21**: 394-399 [PMID: 17620998 DOI: 10.1097/BOT.0b013e318070c028]

62 **Boyce ST**, Lalley AL. Tissue engineering of skin and regenerative medicine for wound care. *Burns Trauma* 2018; **6**: 4 [PMID: 30009192 DOI: 10.1186/s41038-017-0103-y]

63 **Duncan DI**. Correction of implant rippling using allograft dermis. *Aesthet Surg J* 2001; **21**: 81-84 [PMID: 19331877 DOI: 10.1067/maj.2001.113438]

64 **Baxter RA**. Intracapsular allogenic dermal grafts for breast implant-related problems. *Plast Reconstr Surg* 2003; **112**: 1692-6; discussion 1697 [PMID: 14578804 DOI: 10.1097/01.PRS.0000086365.25453.C3]

65 **Breuing KH**, Warren SM. Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings. *Ann Plast Surg* 2005; **55**: 232-239 [PMID: 16106158 DOI: 10.1097/01.sap.0000168527.52472.3c]

66 **Heidemann LN**, Gunnarsson GL, Salzberg CA, Sørensen JA, Thomsen JB. Complications following Nipple-Sparing Mastectomy and Immediate Acellular Dermal Matrix Implant-based Breast Reconstruction-A Systematic Review and Meta-analysis. *Plast Reconstr Surg Glob Open* 2018; **6**: e1625 [PMID: 29464161 DOI: 10.1097/GOX.0000000000001625]

67 **Nahabedian MY**, Jacobson SR. Two-stage prepectoral breast reconstruction. *Gland Surg* 2019; **8**: 43-52 [PMID: 30842927 DOI: 10.21037/gs.2018.09.04]

68 **Salzberg CA**, Ashikari AY, Berry C, Hunsicker LM. Acellular Dermal Matrix-Assisted Direct-to-Implant Breast Reconstruction and Capsular Contracture: A 13-Year Experience. *Plast Reconstr Surg* 2016; **138**: 329-337 [PMID: 27064232 DOI: 10.1097/PRS.0000000000002331]

69 **Hammond DC**, Schmitt WP, O'Connor EA. Treatment of breast animation deformity in implant-based reconstruction with pocket change to the subcutaneous position. *Plast Reconstr Surg* 2015; **135**: 1540-1544 [PMID: 26017590 DOI: 10.1097/PRS.0000000000001277]

70 **Hester TR Jr**, Ghazi BH, Moyer HR, Nahai FR, Wilton M, Stokes L. Use of dermal matrix to prevent capsular contracture in aesthetic breast surgery. *Plast Reconstr Surg* 2012; **130**: 126S-136S [PMID: 23096962 DOI: 10.1097/PRS.0b013e3182605d18]

71 **Sigalove S**, Maxwell GP, Sigalove NM, Storm-Dickerson TL, Pope N, Rice J, Gabriel A. Prepectoral Implant-Based Breast Reconstruction: Rationale, Indications, and Preliminary Results. *Plast Reconstr Surg* 2017; **139**: 287-294 [PMID: 28121858 DOI: 10.1097/PRS.0000000000002950]

72 **Chopra S**, Al-Ishaq Z, Vidya R. The Journey of Prepectoral Breast Reconstruction through Time. *World J Plast Surg* 2021; **10**: 3-13 [PMID: 34307092]

73 **Haddock NT**, Kadakia Y, Liu Y, Teotia SS. Prepectoral versus Subpectoral Tissue Expander Breast Reconstruction: A Historically Controlled, Propensity Score-Matched Comparison of Perioperative Outcomes. *Plast Reconstr Surg* 2021; **148**: 1-9 [PMID: 34003807 DOI: 10.1097/PRS.0000000000008013]

74 **Asaad M**, Yu JZ, Tran JP, Liu J, O'Grady B, Clemens MW, Largo RD, Mericli AF, Schaverien M, Shuck J, Mitchell MP, Butler CE, Selber JC. Surgical and Patient-Reported Outcomes of 694 Two-Stage Prepectoral versus Subpectoral Breast Reconstructions. *Plast Reconstr Surg* 2023; **152**: 43S-54S [PMID: 36877743 DOI: 10.1097/PRS.0000000000010380]

75 **Sbitany H**, Piper M, Lentz R. Prepectoral Breast Reconstruction: A Safe Alternative to Submuscular Prosthetic Reconstruction following Nipple-Sparing Mastectomy. *Plast Reconstr Surg* 2017; **140**: 432-443 [PMID: 28574950 DOI: 10.1097/PRS.0000000000003627]

76 **Xie J**, Wang M, Cao Y, Zhu Z, Ruan S, Ou M, Yu P, Shi J. ADM-assisted prepectoral breast reconstruction is not associated with high complication rate as before: a Meta-analysis. *J Plast Surg Hand Surg* 2023; **57**: 7-15 [PMID: 34581645 DOI: 10.1080/2000656X.2021.1981351]

77 **Brown RH**, Izaddoost S, Bullocks JM. Preventing the "bottoming out" and "star-gazing" phenomena in inferior pedicle breast reduction with an acellular dermal matrix internal brassiere. *Aesthetic Plast Surg* 2010; **34**: 760-767 [PMID: 20602099 DOI: 10.1007/s00266-010-9538-2]

78 **Kaufman D**. Pocket reinforcement using acellular dermal matrices in revisionary breast augmentation. *Clin Plast Surg* 2012; **39**: 137-148 [PMID: 22482355 DOI: 10.1016/j.cps.2012.02.001]

79 **Nahabedian MY**, Spear SL. Acellular dermal matrix for secondary procedures following prosthetic breast reconstruction. *Aesthet Surg J* 2011; **31**: 38S-50S [PMID: 21908823 DOI: 10.1177/1090820X11418093]

80 **Ho G**, Nguyen TJ, Shahabi A, Hwang BH, Chan LS, Wong AK. A systematic review and meta-analysis of complications associated with acellular dermal matrix-assisted breast reconstruction. *Ann Plast Surg* 2012; **68**: 346-356 [PMID: 22421476 DOI: 10.1097/SAP.0b013e31823f3cd9]

81 **Becker S**, Saint-Cyr M, Wong C, Dauwe P, Nagarkar P, Thornton JF, Peng Y. AlloDerm versus DermaMatrix in immediate expander-based breast reconstruction: a preliminary comparison of complication profiles and material compliance. *Plast Reconstr Surg* 2009; **123**: 1-6 [PMID: 19116505 DOI: 10.1097/PRS.0b013e3181904bff]

82 **Sorkin M**, Qi J, Kim HM, Hamill JB, Kozlow JH, Pusic AL, Wilkins EG. Acellular Dermal Matrix in Immediate Expander/Implant Breast Reconstruction: A Multicenter Assessment of Risks and Benefits. *Plast Reconstr Surg* 2017; **140**: 1091-1100 [PMID: 28806288 DOI: 10.1097/PRS.0000000000003842]

83 **Nolan IT**, Farajzadeh MM, Boyd CJ, Bekisz JM, Gibson EG, Salibian AA. Do we need acellular dermal matrix in prepectoral breast reconstruction? A systematic review and meta-analysis. *J Plast Reconstr Aesthet Surg* 2023; **86**: 251-260 [PMID: 37793198 DOI: 10.1016/j.bjps.2023.09.042]

84 **Cothren CC**, Gallego K, Anderson ED, Schmidt D. Chest wall reconstruction with acellular dermal matrix (AlloDerm) and a latissimus muscle flap. *Plast Reconstr Surg* 2004; **114**: 1015-1017 [PMID: 15468424 DOI: 10.1097/01.prs.0000138709.06161.1b]

85 **Sodha NR**, Azoury SC, Sciortino C, Sacks JM, Yang SC. The use of acellular dermal matrices in chest wall reconstruction. *Plast Reconstr*

Surg 2012; **130**: 175S-182S [PMID: 23096968 DOI: 10.1097/PRS.0b013e31825f26b7]

86 **Khalil HH**, Kalkat M, Malahias MN, Rhobaye S, Ashour T, Djearaman MG, Naidu B. Chest Wall Reconstruction with Porcine Acellular Dermal Matrix (Strattice) and Autologous Tissue Transfer for High Risk Patients with Chest Wall Tumors. *Plast Reconstr Surg Glob Open* 2018; **6**: e1703 [PMID: 29922541 DOI: 10.1097/GOX.0000000000001703]

87 **Alshehri A**. Chest wall osteochondroma resection with biologic acellular bovine dermal mesh reconstruction in pediatric hereditary multiple exostoses: A case report and review of literature. *World J Clin Cases* 2023; **11**: 4123-4132 [PMID: 37388792 DOI: 10.12998/wjcc.v11.i17.4123]

88 **Delgado-Miguel C**, Miguel-Ferrero M, Muñoz-Serrano A, Díaz M, López-Gutiérrez JC, Torre C. The Use of Acellular Dermal Matrix (Integra Single Layer) for the Correction of Malformative Chest Wall Deformities: First Case Series Reported. *Surg J (N Y)* 2022; **8**: e187-e191 [PMID: 35991489 DOI: 10.1055/s-0042-1755622]

89 **Baumann DP**, Butler CE. Bioprosthetic mesh in abdominal wall reconstruction. *Semin Plast Surg* 2012; **26**: 18-24 [PMID: 23372454 DOI: 10.1055/s-0032-1302461]

90 **Poussier M**, Denève E, Blanc P, Boulay E, Bertrand M, Nedelcu M, Herrero A, Fabre JM, Nocca D. A review of available prosthetic material for abdominal wall repair. *J Visc Surg* 2013; **150**: 52-59 [PMID: 23137644 DOI: 10.1016/j.jviscsurg.2012.10.002]

91 **Cavallaro A**, Lo Menzo E, Di Vita M, Zanghì A, Cavallaro V, Veroux PF, Cappellani A. Use of biological meshes for abdominal wall reconstruction in highly contaminated fields. *World J Gastroenterol* 2010; **16**: 1928-1933 [PMID: 20397274 DOI: 10.3748/wjg.v16.i15.1928]

92 **Doussot A**, Abo-Alhassan F, Derbal S, Fournel I, Kasereka-Kisenge F, Codjia T, Khalil H, Dubuisson V, Najah H, Laurent A, Romain B, Barrat C, Trésallet C, Mathonnet M, Ortega-Deballon P. Indications and Outcomes of a Cross-Linked Porcine Dermal Collagen Mesh (Permacol) for Complex Abdominal Wall Reconstruction: A Multicenter Audit. *World J Surg* 2019; **43**: 791-797 [PMID: 30426186 DOI: 10.1007/s00268-018-4853-x]

93 **Kissane NA**, Itani KMF. A decade of ventral incisional hernia repairs with biologic acellular dermal matrix: what have we learned? *Plast Reconstr Surg* 2012; **130**: 194S-202S [PMID: 23096971 DOI: 10.1097/PRS.0b013e318265a5ec]

94 **Yang F**, Ji-Ye L, Rong L, Wen T. Use of acellular dermal matrix combined with a component separation technique for repair of contaminated large ventral hernias: a possible ideal solution for this clinical challenge. *Am Surg* 2015; **81**: 150-156 [PMID: 25642876]

95 **Albino FP**, Patel KM, Nahabedian MY, Attinger CE, Bhanot P. Immediate, Multistaged Approach to Infected Synthetic Mesh: Outcomes After Abdominal Wall Reconstruction With Porcine Acellular Dermal Matrix. *Ann Plast Surg* 2015; **75**: 629-633 [PMID: 24667884 DOI: 10.1097/SAP.0000000000000186]

96 **Zhong T**, Janis JE, Ahmad J, Hofer SO. Outcomes after abdominal wall reconstruction using acellular dermal matrix: a systematic review. *J Plast Reconstr Aesthet Surg* 2011; **64**: 1562-1571 [PMID: 21624851 DOI: 10.1016/j.bjps.2011.04.035]

97 **Janis JE**, O'Neill AC, Ahmad J, Zhong T, Hofer SOP. Acellular dermal matrices in abdominal wall reconstruction: a systematic review of the current evidence. *Plast Reconstr Surg* 2012; **130**: 183S-193S [PMID: 23096969 DOI: 10.1097/PRS.0b013e3182605cfc]

98 **Sbitany H**, Kwon E, Chern H, Finlayson E, Varma MG, Hansen SL. Outcomes Analysis of Biologic Mesh Use for Abdominal Wall Reconstruction in Clean-Contaminated and Contaminated Ventral Hernia Repair. *Ann Plast Surg* 2015; **75**: 201-204 [PMID: 24317239 DOI: 10.1097/SAP.0000000000000030]

99 **Atema JJ**, Furnée EJ, Maeda Y, Warusavitarne J, Tanis PJ, Bemelman WA, Vaizey CJ, Boermeester MA. Major Complex Abdominal Wall Repair in Contaminated Fields with Use of a Non-cross-linked Biologic Mesh: A Dual-Institutional Experience. *World J Surg* 2017; **41**: 1993-1999 [PMID: 28265733 DOI: 10.1007/s00268-017-3962-2]

100 **Bochicchio GV**, De Castro GP, Bochicchio KM, Weeks J, Rodriguez E, Scalea TM. Comparison study of acellular dermal matrices in complicated hernia surgery. *J Am Coll Surg* 2013; **217**: 606-613 [PMID: 23973102 DOI: 10.1016/j.jamcollsurg.2013.04.041]

101 **Giordano S**, Garvey PB, Baumann DP, Liu J, Butler CE. Primary fascial closure with biologic mesh reinforcement results in lesser complication and recurrence rates than bridged biologic mesh repair for abdominal wall reconstruction: A propensity score analysis. *Surgery* 2017; **161**: 499-508 [PMID: 27810091 DOI: 10.1016/j.surg.2016.08.009]

102 **Huntington CR**, Cox TC, Blair LJ, Schell S, Randolph D, Prasad T, Lincourt A, Heniford BT, Augenstein VA. Biologic mesh in ventral hernia repair: Outcomes, recurrence, and charge analysis. *Surgery* 2016; **160**: 1517-1527 [PMID: 27528210 DOI: 10.1016/j.surg.2016.07.008]

103 **Iacco A**, Adeyemo A, Riggs T, Janczyk R. Single institutional experience using biological mesh for abdominal wall reconstruction. *Am J Surg* 2014; **208**: 480-484; discussion 483 [PMID: 24462172 DOI: 10.1016/j.amjsurg.2013.09.020]

104 **Garvey PB**, Giordano SA, Baumann DP, Liu J, Butler CE. Long-Term Outcomes after Abdominal Wall Reconstruction with Acellular Dermal Matrix. *J Am Coll Surg* 2017; **224**: 341-350 [PMID: 27993696 DOI: 10.1016/j.jamcollsurg.2016.11.017]

105 **Richmond B**, Ubert A, Judhan R, King J, Harrah T, Dyer B, Thompson S. Component separation with porcine acellular dermal reinforcement is superior to traditional bridged mesh repairs in the open repair of significant midline ventral hernia defects. *Am Surg* 2014; **80**: 725-731 [PMID: 25105388]

106 **Lightfoot RW**, Thrash C, Thompson S, Richmond BK. A Comparison of Component Separation With Porcine Acellular Dermal Reinforcement to Bovine Acellular Dermal Matrix in the Repair of Significant Midline Ventral Hernia Defects. *Am Surg* 2023; **89**: 1003-1008 [PMID: 34772290 DOI: 10.1177/00031348211050844]

107 **Hassan AM**, Franco CM, Shah NR, Netherton TJ, Mericli AF, Garvey PP, Schaverien MV, Chang EI, Hanasono MM, Selber JC, Butler CE. Outcomes of Complex Abdominal Wall Reconstruction After Oncologic Resection: 14-Year Experience at an NCI-Designated Cancer Center. *Ann Surg Oncol* 2023; **30**: 3712-3720 [PMID: 36662331 DOI: 10.1245/s10434-023-13098-y]

108 **Giordano S**, Garvey PB, Mericli A, Baumann DP, Liu J, Butler CE. Component Separation Decreases Hernia Recurrence Rates in Abdominal Wall Reconstruction with Biologic Mesh. *Plast Reconstr Surg* 2024; **153**: 717-726 [PMID: 37285202 DOI: 10.1097/PRS.0000000000010810]

109 **Shridharani SM**, Tufaro AP. A systematic review of acelluar dermal matrices in head and neck reconstruction. *Plast Reconstr Surg* 2012; **130**: 35S-43S [PMID: 23096983 DOI: 10.1097/PRS.0b013e31825eff7a]

110 **Kook WS**, Ryu DH, Baek W, Kook HM, Jang YY, Lew DH. Prevention and Resolution of Silicone Implant-Related Problems in Secondary Rhinoplasty Using a Cross-Linked Human Acellular Dermal Matrix. *Plast Reconstr Surg* 2023; **152**: 45-54 [PMID: 36728206 DOI: 10.1097/PRS.0000000000010205]

111 **Fisher M**, Alba B, Ahmad J, Robotti E, Cerkes N, Gruber RP, Rohrich RJ, Bradley JP, Tanna N. Current Practices in Dorsal Augmentation Rhinoplasty. *Plast Reconstr Surg* 2022; **149**: 1088-1102 [PMID: 35259145 DOI: 10.1097/PRS.0000000000009057]

112 **Xu S**, Sun X, Yang N, Yan A. Human-derived acellular dermal matrix may be an alternative to autologous grafts in tympanic membrane reconstruction: systematic review and meta-analysis. *J Otolaryngol Head Neck Surg* 2021; **50**: 43 [PMID: 34229763 DOI: 10.1186/s40463-021-00518-w]

113 **Chai XD**, Jiang H, Tang LL, Zhang J, Yue LF. Factors influencing Frey syndrome after parotidectomy with acellular dermal matrix. *World J Clin Cases* 2024; **12**: 1578-1584 [PMID: 38576730 DOI: 10.12998/wjcc.v12.i9.1578]

114 **Linn YL**, Khoo MSQ, Sultana R, Iyer NG, Dharmawan R. Comparison of the use of allogenic acellular dermal matrix on rates of Frey syndrome post parotidectomy: A systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2022; **134**: 49-56 [PMID: 35431179 DOI: 10.1016/j.oooo.2021.12.123]

115 **Girod DA**, Sykes K, Jorgensen J, Tawfik O, Tsue T. Acellular dermis compared to skin grafts in oral cavity reconstruction. *Laryngoscope* 2009; **119**: 2141-2149 [PMID: 19650133 DOI: 10.1002/lary.20548]

116 **Gilardino MS**, Aldekhayel S, Govshievich A. A Prospective Study Investigating Fistula Rate Following Primary Palatoplasty Using Acellular Dermal Matrix. *Plast Reconstr Surg Glob Open* 2018; **6**: e1826 [PMID: 30276053 DOI: 10.1097/GOX.0000000000001826]

117 **Zang J**, Feng S, Yang H, Guo X. Comparison of xenogeneic acellular dermal matrix and skin grafts in reconstruction of postoperative defects of hypopharyngeal cancer: A retrospective cohort study. *Medicine (Baltimore)* 2020; **99**: e19361 [PMID: 32118779 DOI: 10.1097/MD.0000000000019361]

118 **Yue D**, Wu X, Song H, Zhou Z, Ye M, Zhu M. The Application of the Acellular Dermal Matrix in the Correction of the Tear Trough Deformity. *Aesthetic Plast Surg* 2018; **42**: 1298-1303 [PMID: 30097671 DOI: 10.1007/s00266-018-1191-1]

119 **Warren WL**, Medary MB, Dureza CD, Bellotte JB, Flannagan PP, Oh MY, Fukushima T. Dural repair using acellular human dermis: experience with 200 cases: technique assessment. *Neurosurgery* 2000; **46**: 1391-1396 [PMID: 10834644 DOI: 10.1097/00006123-200006000-00020]

120 **Clark JM**, Saffold SH, Israel JM. Decellularized dermal grafting in cleft palate repair. *Arch Facial Plast Surg* 2003; **5**: 40-4; discussion 45 [PMID: 12533137 DOI: 10.1001/archfaci.5.1.40]

121 **Steele MH**, Seagle MB. Palatal fistula repair using acellular dermal matrix: the University of Florida experience. *Ann Plast Surg* 2006; **56**: 50-53; discussion 53 [PMID: 16374096 DOI: 10.1097/01.sap.0000185469.80256.9e]

122 **Helling ER**, Dev VR, Garza J, Barone C, Nelluri P, Wang PT. Low fistula rate in palatal clefts closed with the Furlow technique using decellularized dermis. *Plast Reconstr Surg* 2006; **117**: 2361-2365 [PMID: 16772942 DOI: 10.1097/01.prs.0000218788.44591.f0]

123 **Kridel RW**, Foda H, Lunde KC. Septal perforation repair with acellular human dermal allograft. *Arch Otolaryngol Head Neck Surg* 1998; **124**: 73-78 [PMID: 9440784 DOI: 10.1001/archotol.124.1.73]

124 **Conrad DJ**, Zhang H, Côté DWJ. Acellular Human Dermal Allograft as a Graft for Nasal Septal Perforation Reconstruction. *Plast Reconstr Surg* 2018; **141**: 1517-1524 [PMID: 29579028 DOI: 10.1097/PRS.0000000000004410]

125 Choi J, Lee T, Hong J, Kim J, Jeong W, Jo T, Park SW. Complete Preservation of Orbital Fat by Restoration of Attenuated Orbital Septa Using an Acellular Dermal Matrix in Lower Blepharoplasty. *Aesthetic Plast Surg* 2024; **48**: 1537-1546 [PMID: 38334788 DOI: 10.1007/s00266-023-03845-7]

126 **Grumbine FL**, Idowu O, Kersten RC, Deparis SW, Vagefi MR. Correction of Lower Eyelid Retraction with En Glove Placement of Porcine Dermal Collagen Matrix Implant. *Plast Reconstr Surg* 2019; **143**: 743-746 [PMID: 30817645 DOI: 10.1097/PRS.0000000000005376]

127 **Tuan HT**, Ai LD, Ngoc NA, Huong NTL, Vinh VQ, Van Anh T. Expanded Polytetrafluoroethylene Combined with Human Acellular Dermis Matrix for the Nasal Reconstruction in Patients with Postoperative Deformities. *Aesthetic Plast Surg* 2024 [PMID: 39103643 DOI: 10.1007/s00266-024-04277-7]

128 **Acevedo DC**, Shore B, Mirzayan R. Orthopedic applications of acellular human dermal allograft for shoulder and elbow surgery. *Orthop Clin North Am* 2015; **46**: 377-388, x [PMID: 26043051 DOI: 10.1016/j.ocl.2015.02.006]

129 **Neumann JA**, Zgonis MH, Rickert KD, Bradley KE, Kremen TJ, Boggess BR, Toth AP. Interposition Dermal Matrix Xenografts: A Successful Alternative to Traditional Treatment of Massive Rotator Cuff Tears. *Am J Sports Med* 2017; **45**: 1261-1268 [PMID: 28141953 DOI: 10.1177/0363546516683945]

130 **Mirzayan R**, Stone MA, Batech M, Acevedo DC, Singh A. Failed Dermal Allograft Procedures for Irreparable Rotator Cuff Tears Can Still Improve Pain and Function: The "Biologic Tuberoplasty Effect". *Orthop J Sports Med* 2019; **7**: 2325967119863432 [PMID: 31457066 DOI: 10.1177/2325967119863432]

131 **Cole W**, Samsell B, Moore MA. Achilles Tendon Augmented Repair Using Human Acellular Dermal Matrix: A Case Series. *J Foot Ankle Surg* 2018; **57**: 1225-1229 [PMID: 29779989 DOI: 10.1053/j.jfas.2018.03.006]

132 **Shim HS**, Park KS, Kim SW. Preventing postoperative adhesions after hand tendon repair using acellular dermal matrix. *J Wound Care* 2021; **30**: 890-895 [PMID: 34747219 DOI: 10.12968/jowc.2021.30.11.890]

133 **Kokkalis ZT**, Zanaros G, Sotereanos DG. Ligament reconstruction with tendon interposition using an acellular dermal allograft for thumb carpometacarpal arthritis. *Tech Hand Up Extrem Surg* 2009; **13**: 41-46 [PMID: 19276927 DOI: 10.1097/BTH.0b013e31818be857]

134 **Rabinovich RV**, Lee SJ. Proximal Row Carpectomy Using Decellularized Dermal Allograft. *J Hand Surg Am* 2018; **43**: 392.e1-392.e9 [PMID: 29618419 DOI: 10.1016/j.jhsa.2018.01.012]

135 **Hoang D**, Steven P, Chen VW, Stasiak A, Cohen M, Kulber DA. Use of Acellular Dermal Matrix Following Fasciectomy for the Treatment of Dupuytren's Disease. *Plast Reconstr Surg Glob Open* 2019; **7**: e2263 [PMID: 31333979 DOI: 10.1097/GOX.0000000000002263]

136 **Dasgupta A**, Orgill D, Galiano RD, Zelen CM, Huang YC, Chnari E, Li WW. A Novel Reticular Dermal Graft Leverages Architectural and Biological Properties to Support Wound Repair. *Plast Reconstr Surg Glob Open* 2016; **4**: e1065 [PMID: 27826469 DOI: 10.1097/GOX.0000000000001065]

137 **Lafosse A**, Desmet C, Aouassar N, André W, Hanet MS, Beauloye C, Vanwijck R, Poirel HA, Gallez B, Dufrane D. Autologous Adipose Stromal Cells Seeded onto a Human Collagen Matrix for Dermal Regeneration in Chronic Wounds: Clinical Proof of Concept. *Plast Reconstr Surg* 2015; **136**: 279-295 [PMID: 25946602 DOI: 10.1097/PRS.0000000000001437]

138 **Schönmeyr B**, Clavin N, Avraham T, Longo V, Mehrara BJ. Synthesis of a tissue-engineered periosteum with acellular dermal matrix and cultured mesenchymal stem cells. *Tissue Eng Part A* 2009; **15**: 1833-1841 [PMID: 19125645 DOI: 10.1089/ten.tea.2008.0446]

139 **Nyame TT**, Chiang HA, Leavitt T, Ozambela M, Orgill DP. Tissue-Engineered Skin Substitutes. *Plast Reconstr Surg* 2015; **136**: 1379-1388 [PMID: 26595026 DOI: 10.1097/PRS.0000000000001748]

140 **Hammer D**, Rendon JL, Sabino J, Latham K, Fleming ME, Valerio IL. Restoring full-thickness defects with spray skin in conjunction with dermal regenerate template and split-thickness skin grafting: a pilot study. *J Tissue Eng Regen Med* 2017; **11**: 3523-3529 [PMID: 28326683 DOI: 10.1002/term.2264]

141 **Dearman BL**, Stefani K, Li A, Greenwood JE. "Take" of a polymer-based autologous cultured composite "skin" on an integrated temporizing dermal matrix: proof of concept. *J Burn Care Res* 2013; **34**: 151-160 [PMID: 23292583 DOI: 10.1097/BCR.0b013e31828089f9]

142 **Greenwood JE**, Dearman BL. Comparison of a sealed, polymer foam biodegradable temporizing matrix against Integra® dermal regeneration

template in a porcine wound model. *J Burn Care Res* 2012; **33**: 163-173 [PMID: 22002205 DOI: 10.1097/BCR.0b013e318233fac1]

143 **Li A**, Dearman BL, Crompton KE, Moore TG, Greenwood JE. Evaluation of a novel biodegradable polymer for the generation of a dermal matrix. *J Burn Care Res* 2009; **30**: 717-728 [PMID: 19506497 DOI: 10.1097/BCR.0b013e3181abffca]

144 **Rojas-Canales D**, Walters SN, Penko D, Cultrone D, Bailey J, Chtanova T, Nitschke J, Johnston J, Kireta S, Loudovaris T, Kay TW, Kuchel TR, Hawthorne W, O'Connell PJ, Korbutt G, Greenwood JE, Grey ST, Drogemuller CJ, Coates PT. Intracutaneous Transplantation of Islets Within a Biodegradable Temporizing Matrix as an Alternative Site for Islet Transplantation. *Diabetes* 2023; **72**: 758-768 [PMID: 36929171 DOI: 10.2337/db21-0841]

145 **Clarke BM**, Kireta S, Johnston J, Christou C, Greenwood JE, Hurtado PR, Manavis J, Coates PT, Torpy DJ. In Vivo Formation of Adrenal Organoids in a Novel Porcine Model of Adrenocortical Cell Transplantation. *Endocrinology* 2024; **165** [PMID: 39028678 DOI: 10.1210/endocr/bqae086]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6808-6814

DOI: 10.12998/wjcc.v12.i35.6808

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Comprehensive epidemiological assessment of trauma incidents at a level I trauma center

Zhao-Yin Su, Hui Wei, Wei-Ning Wang, Yi-Feng Lin, Yu-Li He, Yao Liu, Ru-Bing Lin, Ya-Tao Liu, Nerich Michael

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 B
Scientific Significance: Grade C

P-Reviewer: Gupta L

Received: July 1, 2024
Revised: August 12, 2024
Accepted: August 27, 2024
Published online: December 16, 2024
Processing time: 115 Days and 5.9 Hours

Zhao-Yin Su, Yi-Feng Lin, Yu-Li He, Yao Liu, The First Clinical College of Medicine, Lanzhou University, Lanzhou 730000, Gansu Province, China

Hui Wei, Wei-Ning Wang, School of Stomatology, Lanzhou University, Lanzhou 730000, Gansu Province, China

Ru-Bing Lin, Department of Orthopedics, Shenzhen Children's Hospital, Shenzhen 518000, Guangdong Province, China

Ya-Tao Liu, Department of Anesthesia, First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China

Nerich Michael, Department of Trauma Surgery, University Hospital Regensburg, Regensburg 93053, Bavaria, Germany

Co-first authors: Zhao-Yin Su and Hui Wei.

Corresponding author: Ya-Tao Liu, MD, Chief Doctor, Department of Anesthesia, First Hospital of Lanzhou University, No. 199 Donggang West Road, Chengguan District, Lanzhou 730000, Gansu Province, China. doctorliuyt@163.com

Abstract

BACKGROUND

The continuous development of social and economic progress and ongoing enhancement of infrastructure construction has led to drastic changes in the occurrence of trauma.

AIM

To analyze the epidemiological characteristics of trauma in Lanzhou City to provide theoretical references for improving quality of trauma care.

METHODS

A retrospective analysis of clinical data from 16585 trauma patients treated at the First Hospital of Lanzhou University Trauma Center from November 1, 2021 to October 31, 2023 was conducted. Data including age, sex, time of trauma, cause of trauma, and major injured body parts were statistically analyzed.

RESULTS

A total of 18235 patients were admitted, with complete data for 16585 cases. Of these, 9793 were male and 6792 were female (male-to-female ratio of 1.44:1). The peak times for trauma occurrence were 10 AM-12 PM and 6-10 PM, and the peak months were from May to October. The leading causes of trauma were falls (45.32%), other trauma (15.88%), road traffic accidents (15.15%), violence (10.82%), cutting/stabbing (9.41%), mechanical injuries (2.65%), winter sports injuries (0.36%), animal bites (0.22%), burns (0.09%), and electrical injuries (0.02%). The distribution of majorly injured body parts showed statistical significance, with limbs/skin being the most affected followed by the head/neck, chest/abdomen, and back.

CONCLUSION

Medical institutions and government agencies can implement preventive measures and policies based on the characteristics of trauma determined in this study to enhance the quality and level of trauma care.

Key Words: Trauma and injury; Injury; Trauma center; Epidemiology; Disease analysis

Core Tip: The data analyzed in this study revealed that the incidence of trauma is higher in males than females and that falls are the primary cause of trauma. The incidence of trauma peaks in the summer and autumn seasons compared to winter and spring and during periods of increased activity throughout the day. Limb and skin traumas were the most common. These findings can serve as guidelines for medical institutions and government agencies to improve the quality and standards of trauma care. Implementation of targeted preventive measures and policies tailored to the characteristics of trauma will be beneficial.

Citation: Su ZY, Wei H, Wang WN, Lin YF, He YL, Liu Y, Lin RB, Liu YT, Michael N. Comprehensive epidemiological assessment of trauma incidents at a level I trauma center. *World J Clin Cases* 2024; 12(35): 6808-6814
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6808.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6808

INTRODUCTION

As socioeconomic conditions continue to improve and infrastructure development accelerates, there has been a consistent year-on-year increase in accidental injuries[1]. Trauma is a significant contributor to mortality, accounting for 9% of global fatalities, and it represents the leading cause of death among younger populations[2]. Survivors often face extended rehabilitation periods and difficulties returning to their previous lives, which imposes a considerable socioeconomic burden[3]. Research in traumatic epidemiology is of paramount importance due to the profound impact of trauma on individuals and society[4,5]. The value of trauma databases in patient management has been well-documented and has underscored their role in improving care[6,7].

Despite significant advancements in trauma medicine globally, China remains in the early stages of developing specialized trauma departments. The First Hospital of Lanzhou University, located in northwestern China, serves as a critical medical center for Lanzhou city and Gansu province. Since June 2021, it has implemented a comprehensive trauma registration system and maintains a dedicated trauma database. To address the disparity between trauma medicine development in China and global standards, we conducted a retrospective analysis of trauma cases from our hospital database. This study aimed to elucidate the epidemiological characteristics of these cases with the goal of enhancing trauma care quality and reducing mortality and disability rates.

MATERIALS AND METHODS

Data sources

The data utilized in this study were sourced from the trauma database of the First Hospital of Lanzhou University, which is recognized as a Gansu Provincial Level I Trauma Center. Stringent quality control measures were implemented to ensure the integrity and precision of the dataset. We analyzed the comprehensive information on all trauma patients admitted to the hospital from November 1, 2021 to October 31, 2023, which totaled 18235 individuals. The exported dataset included essential demographic factors such as age, sex, cause of trauma, and major injured body parts. The dataset underwent careful screening to exclude patients with incomplete data. After completing the data exclusion process, a total of 16585 patients with complete information were retained for analysis. This study received an ethical exemption from the Ethics Committee of the First Hospital of Lanzhou University because of its retrospective design, which did not disclose any patient information.

Study methods

The identification of trauma causes adhered to the classification method prescribed by the Medical Priority Dispatch System. Concurrently, the allocation of trauma sites followed the methodology delineated in the Trauma Index[8]. A categorization strategy was employed, wherein the aggregate occurrences of trauma with unspecified causes or sites were collectively designated as 'other trauma'. This all-encompassing category included a diverse range of trauma types for which specific details about either the cause or the site were indeterminable.

Statistical analysis

Descriptive statistical analysis was conducted using Microsoft Excel 16.0 and SPSS 27.0 software (IBM Corp., Armonk, NY, United States). Various parameters, including the month of trauma occurrence, temporal distribution, composition of trauma causes, distribution of major injured body parts, and patient age, were systematically documented. Intergroup comparisons were performed using χ^2 analysis, with statistical significance set at $P < 0.05$. When conducting multiple comparisons Bonferroni correction was employed to address the potential of increasing the probability of type I errors (false positives).

RESULTS

Basic information

Between November 1, 2021 and October 31, 2023, a total of 16585 trauma patients with complete data were admitted to our trauma center. Among them, 9793 were male and 6792 were female, resulting in a male-to-female ratio of 1.44:1. The age of the patients ranged from 1-month-old to 97-years-old, with a mean age of 34.17 ± 20.90 years. The age range for males was 1-year-old to 95-years-old, with a mean age of 31.91 ± 19.78 years, while the age range of females was 1-month-old to 97-years-old, with a mean age of 37.43 ± 22.01 years.

Temporal distribution

The distribution of trauma incidents demonstrated a diurnal pattern, with the lowest incidence recorded in the early morning hours. A notable increase in trauma cases was observed during two distinct periods: Between 10 AM and 12 PM; and later, between 6 PM and 10 PM. There was a significant increase in trauma cases from May to October, with the peak in August and September. Conversely, the winter months from November to February exhibited a marked decrease in the number of trauma cases, as detailed in Table 1.

Distribution of causes of trauma

Falls were the cause of most of the trauma cases followed by other trauma, road traffic accidents, violence, cutting/stabbing, mechanical injuries, winter sports injuries, animal bites, burns, and electrical injuries. There were 3399 cases in the 14 years and below age group, 4346 cases in the 15-30 years age group, 3792 cases in the 31-44 years age group, 3055 cases in the 45-59 years age group, and 1993 cases in the 60 years and above age group. For all causes of injury, the number of male patients was higher than female, except in cases of animal bites. Additionally, the male-to-female ratio of trauma cases was 1.28:1, which was the only cause of trauma that was lower than the overall ratio of 1.44:1 in all patients. This indicates that there are sex differences in the distribution of trauma causes, with most causes more prevalent in males. More details can be found in Table 2.

Distribution of major injured body parts

The data indicated that injuries to the limbs and skin were the most common, followed by those to the head and neck. Trauma to the chest and abdomen occurred less frequently than head and neck injuries, and back traumas were the rarest. This pattern of injury incidence was statistically significant ($P < 0.001$), highlighting considerable differences in both the prevalence and types of injuries related to different causes. Detailed information on the incidence of each majorly injured body part is provided in Table 3.

DISCUSSION

Characteristics of trauma cases

From November 1, 2021 to October 31, 2023, a cohort of 16585 trauma patients was analyzed, with a predominant representation of young and middle-aged adults, which aligns with several global research findings[3,9-14]. The incidence of trauma in the 15-59 years age group accounted for 69.84% of all cases. Our group surpassed the incidence for this population (63.35%) in another study[15]. In contrast, children aged 0-14 years, who make up 17.95% of the population in China[15], represented 20.49% of the trauma cases in our institution. The elderly population, aged ≥ 60 years, constituted 18.70% of the population in China but accounted for only 12.02% of the trauma cases observed[15].

These data suggest a higher incidence of trauma among the younger population compared to the elderly population, potentially correlating with their occupational engagement and frequent participation in social activities. The 15-30 years age group is arguably the most active group and unsurprisingly constituted the largest percentage of trauma cases. Individuals in this age bracket are often the only children in their family due to the historical one-child policy. This results

Table 1 Time distribution of trauma

Months/hours	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16	16-18	18-20	20-22	22-24	Total
Jan	66	27	23	10	62	88	66	78	104	107	128	90	811
Feb	70	29	15	15	99	102	93	97	88	128	135	86	956
Mar	65	43	22	17	128	146	128	140	135	192	204	111	1331
Apr	79	51	15	25	128	193	132	140	145	189	198	121	1416
May	122	57	20	34	150	203	167	177	189	280	229	155	1783
Jun	118	57	37	27	155	221	189	165	190	273	230	173	1835
Jul	111	66	43	35	160	211	180	178	197	224	272	150	1827
Aug	129	55	41	25	223	267	198	197	195	226	296	193	2045
Sep	92	52	36	38	242	261	201	249	234	302	277	185	2169
Oct	110	45	24	27	157	259	218	204	216	270	236	131	1897
Nov	11	6	3	2	17	43	42	27	42	36	24	11	264
Dec	17	8	4	2	28	35	26	33	35	26	20	17	251
Total	989	496	283	257	1549	2029	1640	1685	1770	2253	2211	1423	16585

Table 2 Distribution of causes of trauma

Cause of trauma	≤ 14 (age)		15-30 (age)		31-44 (age)		45-59 (age)		≥ 60 (age)		Total		Component ratio (%)	Rank
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female		
Falls	1236	665	973	693	857	606	704	602	455	726	4225	3292	45.32	1
Other trauma	387	200	436	281	289	192	253	222	134	139	1599	1034	15.88	2
Road Traffic Accidents	199	96	361	269	356	279	316	308	170	159	1402	1111	15.15	3
Violence	210	80	388	194	283	199	162	108	48	23	1191	604	10.82	4
Cutting/stabbing	155	58	381	199	259	138	176	98	52	45	1023	538	9.41	5
Mechanical injuries	54	39	65	55	70	32	64	26	19	15	272	167	2.65	6
Winter sports injuries	5	2	21	9	14	2	1	3	2	0	43	16	0.36	7
Animal bite	6	5	5	11	3	4	3	1	0	2	17	20	0.22	8
Burns	3	0	2	0	4	0	2	1	1	2	12	3	0.09	9
Electrical injuries	1	0	0	0	2	0	1	0	0	0	4	0	0.02	10
Total	2257	1142	2634	1712	2337	1455	1683	1372	882	1111	9793	6792	100	

in particularly detrimental outcomes to both their families and society.

Males were more susceptible to trauma than females. Similar research findings have also been reported in multiple countries including the United Kingdom, Germany, and Japan[13,16,17]. This disparity may be attributed to greater involvement in physically demanding and injury-prone sectors such as construction and transportation by males[18].

Temporal analysis revealed that the least number of trauma cases occurred in the early morning hours. The peak times for trauma were observed between 10 AM to 12 PM and 6 PM to 10 PM. The morning peak correlates with high production and traffic activities, increasing the likelihood of trauma incidents. The evening period covers the post-work rush hour and nighttime activities. This increases the chance of traffic accidents and various mishaps, which may significantly escalate trauma occurrences[19,20]. Seasonally, trauma incidents peaked during the summer and autumn months (June to October), with a notable decline in the winter months (November to February). In Lanzhou, the warmer climate and heightened social activities during June to October contribute to a higher rate of trauma incidents.

Falls were the predominant cause of trauma. This is likely a consequence of the varied topography and elevation of Lanzhou coupled with an increase in infrastructure development projects in recent years. Another study from Germany reported that the primary cause of trauma was impact followed by falls, sports injuries, and traffic accidents[17]. Causes of trauma are likely to vary between geographic and cultural regions. Trauma resulting from road traffic is one of the major causes of trauma. Due to the expansion of private vehicle ownership and sustained economic development, road

Table 3 Distribution of trauma sites in patients with different causes of trauma, *n* (%)

Cause of injury	Limbs/skin	Head/neck	Chest/abdomen	Back	Total
Falls	4758 (63.30)	2012 (26.77)	641 (8.53)	286 (3.80)	7517 (100.00)
Other trauma	1576 (59.86)	542 (20.85)	255 (9.68)	92 (3.49)	2633 (100.00)
Road traffic accidents	1399 (55.67)	666 (26.50)	342 (13.61)	106 (4.22)	2513 (100.00)
Violence	581 (32.37)	956 (53.26)	235 (13.09)	23 (1.28)	1795 (100.00)
Cutting/stabbing	1359 (89.37)	142 (9.10)	52 (3.33)	8 (0.51)	1561 (100.00)
Mechanical injuries	293 (66.74)	91 (20.73)	43 (9.79)	12 (2.73)	439 (100.00)
Winter sports injury	43 (72.88)	6 (10.17)	4 (6.78)	6 (10.17)	59 (100.00)
Animal bite	30 (81.08)	4 (10.81)	1 (2.70)	2 (5.88)	37 (100.00)
Burns	9 (60.00)	5 (33.33)	1 (6.66)	0 (0.00)	15 (100.00)
Electrical injuries	4 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (100.00)
Total	10052 (60.61)	4424 (26.67)	1574 (9.49)	535 (3.23)	16585 (100.00)

traffic in the region is becoming increasingly complex, leading to a significant rise in road traffic accidents.

Our study also highlighted significant variations in the body part injured by trauma. These data reveal areas in which trauma centers and hospitals can prepare to effectively treat trauma cases.

Prevention and treatment of trauma

Comprehensive preventive measures are imperative to decrease the incidence of trauma. There is a crucial need to intensify educational efforts and provide adequate safety equipment to increase occupational safety. Moreover, it is essential to bolster the widespread dissemination of information about occupational safety. Equally important is the reinforcement of traffic regulations and the promotion of traffic safety awareness to reduce the incidence of road accidents. The enhancement of civic education would foster a stronger understanding of the legal system among citizens, thereby increasing legal awareness and self-protection measures to diminish the occurrence of adverse events. Caution is advised to prevent injuries from animal bites, including specifically from pets. Pet owners should be reminded that immediate medical attention is necessary in the event of such incidents.

There is an urgent need to improve the trauma registry system and establish a comprehensive trauma database[6,7,20-22]. This involves conducting thorough epidemiological analyses of trauma, thereby facilitating targeted and effective treatment strategies based on the identified patterns and characteristics of trauma incidents[7]. The result of these efforts would enhance the quality of trauma care and minimize the adverse impacts of trauma. This multidimensional approach necessitates collaboration among national entities, society, healthcare institutions, and individuals. The insights gained from epidemiological studies of trauma inform the development of relevant legal frameworks as well as serve as a crucial reference for healthcare facilities to enhance the quality of trauma care.

Prevention and treatment of trauma contributes to alleviating familial and societal pressures. However, it simultaneously requires collective efforts at the national, societal, hospital, and individual levels. Trauma epidemiological analyses summarize the patterns of occurrence and development of trauma, which provides a basis for the formulation of relevant trauma laws and regulations. They also serve as a reference for improving the quality of trauma care in hospitals.

Limitations

This study reported the epidemiological characteristics of a large cohort of patients who experienced trauma. However, it is difficult to conduct large-scale follow-up on these patients due to the mild injuries, short hospital stays, and large number of patients. Therefore, there is still a lack of long-term prognosis and quality of life assessment for trauma patients. Long-term studies of treated patients who experienced trauma should include assessments of quality of life, functional recovery, and mental health. These types of studies will lead to a better understanding of treatment effectiveness and can provide comprehensive rehabilitation support for patients.

CONCLUSION

Trauma predominantly affects young and middle-aged individuals, with a higher incidence observed in males compared to females. Among the various mechanisms of trauma, falls were identified as the leading cause of trauma. Seasonal variations in trauma incidence revealed that injuries are more prevalent during the summer and autumn months, and the frequency of trauma cases peaked during periods of increased human activity throughout the day. Limb/skin trauma were the most common locations of trauma injuries. To address these patterns, medical institutions and government agencies should implement targeted preventive measures and policies tailored to the specific characteristics of trauma. These strategies could significantly improve the quality and effectiveness of trauma care, ultimately enhancing patient

outcomes.

FOOTNOTES

Author contributions: Su ZY, Wei H, Wang WN, Lin YF, Liu YT, and Michael N designed the research study; Su ZY, Wei H, Wang WN, Lin YF, and He YL performed the research; Liu Y, Lin RB, Liu YT, and Michael N contributed new reagents and analytic tools; Su ZY, Wei H, Wang WN, and Lin YF analyzed the data and wrote the manuscript. All authors read and approved the final manuscript. Su ZY and Wei H are co-first authors of this study, reflecting the equal importance of their contributions. Su ZY was responsible for the experimental design and data collection of this study. He led the planning and execution of the experiments and provided solutions to key technical issues during data collection. Additionally, Su ZY participated in the preliminary data analysis and the creation of charts, offering valuable perspectives for data interpretation. Wei H was responsible for data analysis and manuscript writing. She applied advanced statistical methods to thoroughly analyze the experimental data, ensuring the accuracy and scientific validity of the results. Wei H was also the principal writer of the manuscript, responsible for organizing the research findings and composing the discussion section, clearly articulating the scientific significance and practical applications of the research findings. Both authors engaged in frequent discussions and collaborations throughout the research process, jointly discussing the direction of the research and interpretation of the results, ensuring the high-quality completion of the study. Each author made indispensable contributions within their areas of expertise, collectively driving the success of the research project.

Supported by Ministry of Science and Technology Senior Foreign Expert Program, No. G2019028023 and No. G2020028007; National College Student Innovation and Entrepreneurship Program, No. 202210730172; Medical Innovation and Development Project of Lanzhou University, No. lzuyxcx-2022-99; and Joint Research Fund Project of Gansu Province, No. 23JRRA1496.

Institutional review board statement: This study received an ethical exemption from the Ethics Committee of the First Hospital of Lanzhou University because its retrospective design and did not disclose any patient information.

Informed consent statement: No information about the corresponding subjects was involved in this study.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Country of origin: China

ORCID number: Zhao-Yin Su 0009-0007-0037-0529; Ya-Tao Liu 0000-0002-7423-0090.

S-Editor: Qu XL
L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **Benhamed A**, Ndiaye A, Emond M, Lieutaud T, Boucher V, Gossiome A, Laumon B, Gadegbeku B, Tazarourte K. Road traffic accident-related thoracic trauma: Epidemiology, injury pattern, outcome, and impact on mortality-A multicenter observational study. *PLoS One* 2022; **17**: e0268202 [PMID: 35522686 DOI: 10.1371/journal.pone.0268202]

2 **Candefjord S**, Asker L, Caragounis EC. Mortality of trauma patients treated at trauma centers compared to non-trauma centers in Sweden: a retrospective study. *Eur J Trauma Emerg Surg* 2022; **48**: 525-536 [PMID: 32719897 DOI: 10.1007/s00068-020-01446-6]

3 **Heim C**, Bosisio F, Roth A, Bloch J, Borens O, Daniel RT, Denys A, Oddo M, Pasquier M, Schmidt S, Schoettker P, Zingg T, Wasserfallen JB. Is trauma in Switzerland any different? epidemiology and patterns of injury in major trauma - a 5-year review from a Swiss trauma centre. *Swiss Med Wkly* 2014; **144**: w13958 [PMID: 24706486 DOI: 10.4414/smw.2014.13958]

4 **Artuso CE**. Rural trauma challenges in Alaska. *Crit Care Nurs Clin North Am* 2012; **24**: 593-600 [PMID: 23089663 DOI: 10.1016/j.ccell.2012.07.004]

5 **Morgan JM**, Calleja P. Emergency trauma care in rural and remote settings: Challenges and patient outcomes. *Int Emerg Nurs* 2020; **51**: 100880 [PMID: 32622226 DOI: 10.1016/j.ienj.2020.100880]

6 **Prionas A**, Tsoulfas G, Tooulias A, Papakoulas A, Piachas A, Papadopoulos V. Evaluating trauma care, outcomes and costs in a system in crisis: the necessity of a Greek National Trauma Database. *Trauma Surg Acute Care Open* 2020; **5**: e000401 [PMID: 32373714 DOI: 10.1136/tsaco-2019-000401]

7 **Alao DO**, Cevik AA, Eid HO, Jummani Z, Abu-Zidan FM. Trauma system developments reduce mortality in hospitalized trauma patients in Al-Ain City, United Arab Emirates, despite increased severity of injury. *World J Emerg Surg* 2020; **15**: 49 [PMID: 32811505 DOI: 10.1186/s13017-020-00327-y]

8 **Smith JS Jr**, Bartholomew MJ. Trauma index revisited: a better triage tool. *Crit Care Med* 1990; **18**: 174-180 [PMID: 2298010 DOI: 10.1097/00003246-199002000-00010]

9 **Kundavaram PPA**, Jindal A, Hazra D, Biju A, Raju F, Samarpit CC. A Retrospective analysis of the profile of trauma victims presenting to an emergency department in South India. *J Family Med Prim Care* 2022; **11**: 1907-1912 [PMID: 35800479 DOI: 10.4103/jfmpc.jfmpc_1896_21]

10 **Chaudhari PP**, Anderson M, Ourshalimian S, Goodhue C, Sudharshan R, Valadez S, Spurrier R. Epidemiology of pediatric trauma during the coronavirus disease-2019 pandemic. *J Pediatr Surg* 2022; **57**: 284-290 [PMID: 34742575 DOI: 10.1016/j.jpedsurg.2021.09.054]

11 **Mazzolini K**, Dzubnar J, Kwak H, Banks K, Mooney C, Tang A, Cohan C, Browder T. An Epidemic Within the Pandemic: The Rising Tide of Trauma During COVID-19. *J Surg Res* 2022; **272**: 139-145 [PMID: 34971837 DOI: 10.1016/j.jss.2021.11.016]

12 **Bashiri A**, Morada A, Sultany M, Senepathi S, Silverman S, Casós S, Behm R. Trends of Trauma Admissions in a Rural Trauma Center During Coronavirus Disease 2019 Pandemic. *J Surg Res* 2023; **289**: 202-210 [PMID: 37141703 DOI: 10.1016/j.jss.2023.02.040]

13 **Aoki M**, Abe T, Saitoh D, Oshima K. Epidemiology, Patterns of treatment, and Mortality of Pediatric Trauma Patients in Japan. *Sci Rep* 2019; **9**: 917 [PMID: 30696939 DOI: 10.1038/s41598-018-37579-3]

14 **Cintean R**, Eickhoff A, Zieger J, Gebhard F, Schütze K. Epidemiology, patterns, and mechanisms of pediatric trauma: a review of 12,508 patients. *Eur J Trauma Emerg Surg* 2023; **49**: 451-459 [PMID: 36001123 DOI: 10.1007/s00068-022-02088-6]

15 Communiqué of the Seventh National Population Census (No. 5). Available from: https://www.stats.gov.cn/english/PressRelease/202105/t20210510_1817190.html

16 **Naqvi G**, Johansson G, Yip G, Rehm A, Carrothers A, Stöhr K. Mechanisms, patterns and outcomes of paediatric polytrauma in a UK major trauma centre. *Ann R Coll Surg Engl* 2017; **99**: 39-45 [PMID: 27490985 DOI: 10.1308/rcsann.2016.0222]

17 **Voth M**, Lustenberger T, Auner B, Frank J, Marzi I. What injuries should we expect in the emergency room? *Injury* 2017; **48**: 2119-2124 [PMID: 28778731 DOI: 10.1016/j.injury.2017.07.027]

18 **Zheng DJ**, Sur PJ, Ariokot MG, Juillard C, Ajiko MM, Dicker RA. Epidemiology of injured patients in rural Uganda: A prospective trauma registry's first 1000 days. *PLoS One* 2021; **16**: e0245779 [PMID: 33481891 DOI: 10.1371/journal.pone.0245779]

19 **Abhilash KP**, Chakraborthy N, Pandian GR, Dhanawade VS, Bhanu TK, Priya K. Profile of trauma patients in the emergency department of a tertiary care hospital in South India. *J Family Med Prim Care* 2016; **5**: 558-563 [PMID: 28217583 DOI: 10.4103/2249-4863.197279]

20 **Liu JY**, Hu QL, Ko CY. Databases for surgical health services research: National Trauma Data Bank and Trauma Quality Improvement Program. *Surgery* 2018; **164**: 919-920 [PMID: 29429579 DOI: 10.1016/j.surg.2017.12.030]

21 **Lanitis S**, Kontovounisios C, Zafeiriadou P, Sgourakis G, Karkoulias K, Armoutides V, Papaconstandinou T, Karaliotas C. Epidemiology and management of trauma patients in a Greek multispecialty hospital in the absence of a dedicated trauma center. *Eur J Trauma Emerg Surg* 2013; **39**: 369-374 [PMID: 26815397 DOI: 10.1007/s00068-012-0221-y]

22 **Haider AH**, Saleem T, Leow JJ, Villegas CV, Kisat M, Schneider EB, Haut ER, Stevens KA, Cornwell EE 3rd, MacKenzie EJ, Efron DT. Influence of the National Trauma Data Bank on the study of trauma outcomes: is it time to set research best practices to further enhance its impact? *J Am Coll Surg* 2012; **214**: 756-768 [PMID: 22321521 DOI: 10.1016/j.jamcollsurg.2011.12.013]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6815-6825

DOI: 10.12998/wjcc.v12.i35.6815

ISSN 2307-8960 (online)

SYSTEMATIC REVIEWS

Gut microbiota changes associated with frailty in older adults: A systematic review of observational studies

Na-Na Wen, Li-Wei Sun, Qian Geng, Guo-Hua Zheng

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 B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Duan SL

Received: August 15, 2024

Revised: September 4, 2024

Accepted: September 25, 2024

Published online: December 16, 2024

Processing time: 70 Days and 1.2 Hours

Na-Na Wen, Li-Wei Sun, Qian Geng, Guo-Hua Zheng, College of Nursing and Health Management, Shanghai University of Medicine and Health Sciences, Shanghai 201318, China

Na-Na Wen, Graduate School, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

Corresponding author: Guo-Hua Zheng, PhD, Professor, College of Nursing and Health Management, Shanghai University of Medicine and Health Sciences, No. 279 Zhouzhu Road, Pudong New District, Shanghai 201318, China. zhenggh@sumhs.edu.cn

Abstract

BACKGROUND

Frailty is a complex aging-related syndrome characterized by a cumulative loss of physiological reserve and increased vulnerability to adverse clinical outcomes, including falls, disability, incapacity and death. While an increasing number of studies suggest that the gut microbiota may play a key role in the pathophysiology of frailty, direct evaluation of the association between gut microbiome alterations and frailty in older adults remains limited.

AIM

To gain insight into gut dysbiosis in frail older adults.

METHODS

Seven electronic databases (China National Knowledge Infrastructure, VIP, SinoMed, Wanfang, PubMed, Web of Science and EMBASE) were searched for articles published before October 31, 2023 to identify observational studies that compared the microbiomes of older adults with and without frailty. The diversity and composition of the gut microbiota were the main outcomes used to analyze the associations of changes in the gut microbiota with frailty in older adults. The quality of the included studies was assessed *via* the Newcastle-Ottawa Scale and the Agency for Healthcare Research and Quality.

RESULTS

Eleven observational studies with 912 older adults were included in this review. Consistent results revealed a significant difference in the gut microbiota composition between frail and non-frail older adults, with a significant decrease in α diversity and a significant increase in β diversity in frail older adults. The pooled results revealed that at the phylum level, four microbiota (*Actinobacteria*, *Proteobacteria*, *Verrucomicrobia* and *Synergistetes*) were significantly enriched, and two

microbiota (*Firmicutes* and *Fusobacteria*) were significantly depleted in frail older adults. At the family level, the results consistently revealed that the abundances of 6 families, most of which belong to the *Actinobacteria* or *Proteobacteria* phylum, were greater in frail than in non-frail older adults. At the genus or species level, consistent results from more than two studies revealed that the abundances of the genera *Prevotella*, *Faecalibacterium,* and *Roseburia* were significantly lower in frail older adults; individual studies revealed that the abundances of some genera or species (*e.g.*, *Megamonas*, *Blautia*, and *Megasphaera*) were significantly lower, whereas those of other genera or species (*e.g.*, *Bifidobacterium*, *Oscillospira*, *Ruminococcus* and *Pyramidobacter*) were significantly greater in frail older adults.

CONCLUSION

This systematic review suggests that changes in the gut microbiota are associated with frailty in older adults, which is commonly reflected by a reduction in beneficial species and an increase in pathogenic species. However, further studies are needed to confirm these findings.

Key Words: Frailty; Gut microbiota; Observational study; Older adults; Systematic review

Core Tip: A growing number of studies have reported changes in the composition and diversity of the gut microbiota between frail and healthy older adults, suggesting that alterations in the gut microbiota may play a key role in the pathophysiology of frailty; however, direct assessment of the associations between changes in the gut microbiome and frailty in older adults remains limited. This review revealed a significant decrease in α diversity and a significant increase in β diversity in frail older adults compared with non-frail older adults, which was commonly reflected by a reduction in beneficial species and an increase in pathogenic species. This study provides a comprehensive overview of the relationship between changes in the gut microbiota and frailty in older adults and suggests a possible role for the gut microbiota in the pathogenesis of frailty.

Citation: Wen NN, Sun LW, Geng Q, Zheng GH. Gut microbiota changes associated with frailty in older adults: A systematic review of observational studies. *World J Clin Cases* 2024; 12(35): 6815-6825
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6815.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6815

INTRODUCTION

Frailty is a complex age-related geriatric syndrome characterized by decreased physiological reserves in the body with decreased anti-stress ability and vulnerability in the face of external stimuli, leading to increased risks of multiple adverse health outcomes, including falls, hospitalization, and even mortality[1,2]. Frailty is common among community-dwelling older adults, with a prevalence ranging from 4% to 59% among those aged 65 years and older and 25% among older adults over 85 years[3]. Current studies have shown that the risk factors associated with frailty in older adults are mainly related to increasing age, lower weight, female sex, living alone, low levels of physical activity, polypharmacy, unhealthy lifestyle, smoking, alcohol consumption, and poor diet. These factors interact and form a cycle to cause chronic malnutrition, inflammation, and disruption of hormone regulation[4-7]. Recently, intestinal dysbacteriosis has been newly identified as a risk factor for frailty in older adults[6,8]. For example, a study of 728 female twins revealed a negative association between gut microbiota α diversity and frailty, with increases in *Eubacterium dolichum* and *Eggerthella lenta* in the frail group[9].

The gut microbiota is a relatively stable community consisting of a large number of bacteria, fungi, and viruses that colonize the human gut. Gut dysbiosis has been shown to contribute to human diseases, including metabolic diseases, neurodegenerative disorders, and chronic inflammatory diseases[10-11]. The pathogenesis of frailty syndrome may involve chronic inflammation, immune activation, and the musculoskeletal system[12]. Many studies have shown that the diversity and composition of the gut microbiota are significantly altered in community-dwelling older adults with frailty, which in turn may play an important role in the development of frailty in community-dwelling older adults. For example, one study suggested that an imbalance in the gut microbiota triggers an inflammatory response, leading to an increase in intestinal permeability and the entry of pathogen-associated antibodies into the circulation[6,13]. However, most of the previous studies on frailty and the gut microbiota have only examined changes in the composition of bacterial species, but the characteristics of the gut microbiota of frail older people are still unclear, although interest in this topic is increasing. Therefore, there is a lack of adequate evidence on changes in the gut microbiota and frailty in older adults. This systematic literature review mainly summarizes the associations between changes in the gut microbiota and frailty in people over 60 years of age.

MATERIALS AND METHODS

Search strategy

Seven databases (PubMed, EMBASE, Web of Science, SinoMed, China National Knowledge Infrastructure, VIP, and Wanfang) were used to search for Chinese and English articles, respectively, using Medical Subject Headings terms or free words (*e.g.*, "gastrointestinal microbiome" or "gut microbiota" or "intestinal microbiomes" or "gastric microbiome" or "enteric bacteria" or "gut microbiome") and ("frailty" or "frailty syndrome" or "frailties" or "frail elder"). The final search began in October 2023, with no publication date restrictions. A summary of the search strategy for the different databases is described in Supplementary Table 1.

Inclusion criteria

Eligible studies were identified according to the following inclusion criteria: (1) Participants were adults over 60 years of age; (2) The profile of the gut microbiota was compared between frail and non-frail older adults; and (3) The primary outcome was the abundance of bacterial phyla, families, genera and species of the human gut microbiota. Studies for which the required data could not be retrieved were excluded.

Study screening, data extraction, and assessment of risk bias

The retrieved records were imported into reference management software (Note Express 3.1) for repeated screening. Two reviewers independently identified the eligibility of the retrieved articles according to the inclusion criteria after the duplicate records were removed. Disagreements were discussed and resolved in consultation with a third reviewer. Data from the eligible studies were extracted by one reviewer *via* prepared data extraction tables and checked by another reviewer. The information extracted included study design, participants, methodological characteristics, sample size, outcomes, and measurement methods. The risk of bias for the eligible studies was assessed *via* the Newcastle-Ottawa Scale (NOS)[14] and the Agency for Healthcare Research and Quality (AHRQ)[15]. Disagreements were resolved by discussion with a third reviewer.

RESULTS

Literature search

A total of 1126 records were found by searching seven electronic databases, and 520 records were deleted because of duplication. A total of 583 studies were excluded based on the title and abstract. The remaining 23 studies were further assessed by reading the full texts. As a result, 12 studies were excluded for various reasons (10 did not match the inclusion criteria, and 2 did not have the full text available). Eleven studies were ultimately included in this review. A detailed flow chart of the literature screening process is shown in Figure 1.

Characteristics of the included studies

Table 1 summarizes the characteristics of the 11 studies included in the systematic review[16-26]. All included studies consisted of 7 cross-sectional studies[16-22], 3 cohort studies[23-25], and 1 case-control study[26], including 912 older adults ranging in age from 65 years to 100 years. Seven studies analyzed the α diversity of the gut microbiota[17-20,22-23,26], whereas seven studies analyzed the β diversity of the gut microbiota[17,19,21-24,26]. For the outcome measures, two studies reported changes in the gut microbiota at the phylum level[17,22], two at the family level[19,22], eight at the genus level[16-22,25], and five at the species level[16,20,23-25]. Among these included studies, seven studies performed genetic analysis of the gut microbiota *via* the 16S rRNA method[17-22,26], three studies used the metagenomic sequencing method[23-25], and one study used the fluorescence in situ hybridization method[16]. The frailty measures used in the included studies varied widely, with the rockwood frailty index[22,25,26], FI[18], Clinical Frailty Scale[23,24], short physical performance battery[19], Groningen Frailty Indicator[16], Fried's definition[17], Fried's Frailty Phenotype[20] and Frailty Phenotype[21] being used. The non-frail controls were mainly healthy older adults.

Quality assessment

Table 2, 3 and 4 summarizes the study quality of the included studies, as assessed by the AHRQ for 7 cross-sectional studies and by the NOS tool for 3 cohort studies and one case-control study[16-21,23-25]. Of the seven cross-sectional studies, six were of moderate quality[16-21], and one was of high quality[22]. All three cohort studies were of moderate quality[23-25], and one case-control study was of high quality [26].

Outcome assessment

Changes in the diversity of the gut microbiota: A total of seven studies analyzed the difference in α diversity of the gut microbiota measured by the Chao index, Simpson index, and Shannon index between frail older adults and non-frail controls[17-20,22,23,26], and two studies reported a significant decrease in frail older adults[18,23]. Seven studies[17,19,21,23,24,26,27] compared the β diversity measured by principal coordinate analysis in frail older adults with that in controls, and two studies reported significantly greater β diversity in frail than non-frail older adults[21,22].

Changes in the gut microbiota composition: Figure 2 summarizes the changes in the gut microbiota composition at each level in frail older adults compared with non-frail older adults. Two studies reported results at the phylum level[17,22],

Table 1 Main characteristics of the included studies in this review

Ref.	Picca *et al*[19], 2020	Van Tongeren *et al*[16], 2005	Xu *et al*[17], 2021	Lim *et al*[18], 2021		Zhang *et al*[22], 2020	Margiotta *et al* [20], 2020	Ticinesi *et al*[26], 2017	Haran *et al* [24], 2018	Haran *et al*[23], 2021	Larson *et al* [25], 2020	Zhang *et al* [21], 2022
Study design	CSS	CSS	CSS	CSS		CSS	CSS	CCS	CHS	CHS	CHS	CSS
Participants	Samples	35	23	94	176	27	64	76	23	166	47	181
	Age (years)	> 70	70-100	80.7 ± 5.7	74.7	81.63 ± 7.90	≥ 65	83.3 ± 7.5	≥ 65	86.2 ± 9.1	> 65	≥ 65
	Male/female	20/15	4/19	44/50	54/122	17/10	43/21	39/37	23	30/136	47	72/109
Genetic analysis	16S rRNA V3-V4	Fluorescence in situ hybridization	16sRNA V3-V4	16S rRNA		16S rRNA	16sRNA V3-V4	16S rRNA	metagenomic sequencing	metagenomic sequencing	metagenomic sequencing	16sRNA V3-V4
Frailty diagnosis	Short physical performance battery	Groningen Frailty Indicator	Fried's definition	Frailty index		Rockwood Frailty Index	Fried's Frailty Phenotype	Rockwood Index	CFS	CFS	Rockwood Index	Frailty Phenotype
Outcome measurement	α-diversity, β-diversity, family level, genus level	Genus level, species level	α-diversity, β-diversity, phylum level, genus level	α-diversity, genus level, dpecies level		α-diversity, β-diversity, phylum level, family level, genus level	α-diversity, phylum level, genus level	α-diversity, β-diversity	β-diversity, species level	α-diversity, β-diversity, species level	Genus level, species level	β-diversity, phylum level, genus level

CSS: Cross-sectional study: CCS: Case-control study; CHS: Cohort study; CFS: Clinical Frailty Scale.

Table 2 The Agency for Healthcare Research and Quality assessment for the cross-sectional study

Ref.	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Scores
Picca *et al*[19], 2020	Yes	Yes		Yes	Yes			Yes		Yes		6
Van Tongeren *et al* [16], 2005	Yes	Yes		Yes	Yes		Yes			Yes		6
Xu *et al*[17], 2021	Yes			Yes	Yes		Yes	Yes		Yes		6
Lim *et al*[18], 2021	Yes	Yes			Yes		Yes	Yes		Yes		6
Zhang *et al*[22], 2020	Yes	Yes		Yes	Yes	Yes	Yes	Yes		Yes		8
Margiotta *et al*[20], 2020	Yes	Yes		Yes	Yes		Yes	Yes		Yes		7
Zhang *et al*[21], 2022	Yes	Yes	Yes		Yes	Yes	Yes	Yes				7

Yes is one point, the total number of stars represents a number of points. Item 1: Define the source of information (survey, record review)? Item 2: Inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications? Item 3: Indicate time period used for identifying patients? Item 4: Indicate whether or not subjects were consecutive if not population-based? Item 5: Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participant? Item 6: Describe any assessments undertaken for quality assurance purposes (*e.g.*, testretest of primary out come measuroments)? Item 7: Explain any patient exclusions from analysis? Item 8: Describe how confounding was assessed and/or controlled? Item 9: If applicable, explain how missing data were handled in the analysis? Item 10: Summarize patient response rates and completeness of data collection? Item 11: Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained?

Table 3 The Newcastle-Ottawa Scale assessment for the cohort studies

Ref.	Selection				Comparability		Exposure			Scores
	Representativeness of selection of the non-exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohort on the basis of the design or analysis	Ascertainment of outcome	Ascertainment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Haran *et al*[24], 2018	Yes	Yes			Yes	Yes, Yes				5
Haran *et al*[23], 2021	Yes	Yes				Yes, Yes		Yes	Yes	6
Larson *et al*[25], 2020	Yes	Yes			Yes	Yes, Yes				5

Yes is one point, the total number of stars represents a number of points.

and all of them reported that frail older adults had a significantly greater relative abundance of the *Actinobacteria* phylum [17,22]. An individual study reported that frail older adults had significantly greater relative abundances of the *Proteobacteria*, *Verrucomicrobia* and *Synergistetes* phyla[17] and significantly lower abundances of the *Firmicutes*[17] and *Fusobacteria* phyla[22].

Two studies reported differences in the gut microbial composition at the family level between frail and non-frail older adults[19,22], with significantly greater abundances of the *Peptostreptococcaceae*[19], *Mogibacteriaceae, Bifidobacteriaceae*[19], *Coriobacteriaceae, Enterobacteriaceae,* and *Moraxellaceae* families[22] in frail older adults.

Eight studies reported changes in gut microbiota composition at the genus level. Three studies reported a significantly lower abundance of the genus *Prevotella* in frail older adults[16-18]; two studies reported that frail older adults presented significantly lower relative abundances of the genera *Faecalibacterium* and *Roseburia*[17,21]. Several individual studies reported that the relative abundances of *Megamonas*, *Blautia*, *Megasphaera*, *Haemophilus*[17], *Adlercreutzia*, *Clostridium*, *Coprococcus*, *Phascolarctobacterium*, *Turicibacter*[21], *Eubacterium*[19], *Gemella, Lachnoanaerobaculum*, *[Eubacterium]_ruminantium_group*, *Tyzzerella*, *Azospira*, *Cloacibacterium and EU455341_g*[22] genera, most of which belong to the

Table 4 The Newcastle-Ottawa Scale assessment for the case-control study

Ref.	Selection				Comparability	Exposure			Scores
	Adequate definition of case	Representativeness of the case	Selection of controls	Definition of controls	Control for important factor	Ascertainment of exposure	Same method of ascertain for cases and controls	Non-responsese rate	
Ticinesi *et al* [26], 2017	Yes	Yes	Yes	Yes	Yes	Yes, Yes		Yes	7

Yes is one point, the total number of stars represents a number of points.

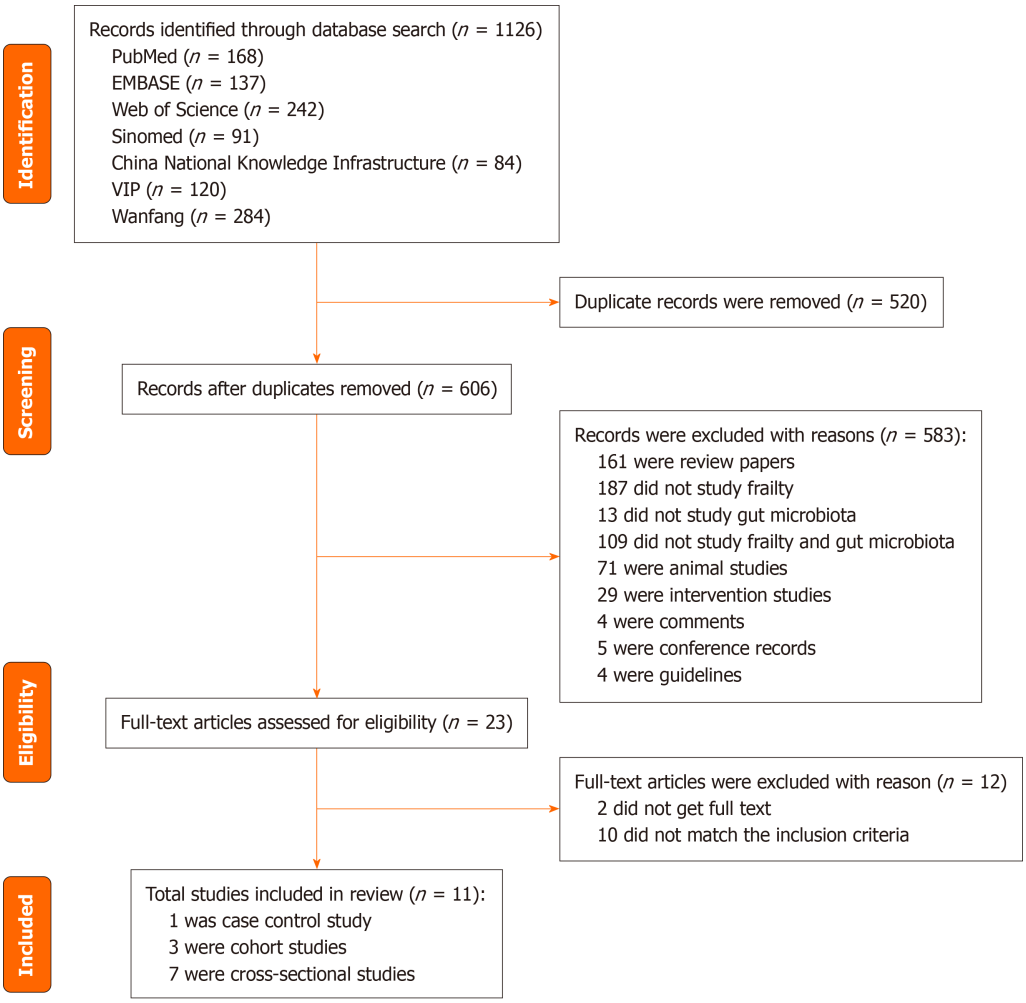

Figure 1 Preferred Items for Systematic Reviews and Meta-Analysis flow diagram of literature search.

Firmicutes phylum, were significantly lower in frail older adults. Moreover, individual studies reported that frail older adults presented increased relative abundances of *Bifidobacterium*[17], *Eggerthella*, *Olsenella*[16], *Atopobium*[22], *Parabacteroides*[17], *Alistipes*[17], *Bacteroides*[18], *Oscillospira*, *Ruminococcus*, *Pyramidobacter* and *Dialister*[19], *Akkermansia* and *Klebsiella*[17], *KF843164_g*, *Pseudoxanthomonas*, *EF434341_g* and *Prevotella_9*[22], and *Oscillospira* and *Coprobacillus*[20]. In addition, the genera of *Lactobacillus* in the included studies were heterogeneous, and three studies[17,20-21] reported a significantly higher relative abundance, but one study[16] reported a significantly lower relative abundance in frail older adults.

At the species level, two studies[16,23] reported that the relative abundance of *Faecalibacterium prausnitzii* was significantly lower in frail than in non-frail older adults. Furthermore, individual studies reported that the abundances of

Figure 2 Changes in the gut microbiota composition in older adults with frailty compared to the controls. Red arrows indicate increasing relative abundance; blue arrows indicate decreasing relative abundance in older adults with frailty compared to the controls; One arrow represents one analyzed study.

the *Prevotella copri*[18], *Coprococcus eutactus*[18], *Bacteroides vulgatus*[23] and *Anaerostipes hadrus* species[23] were significantly lower in frail older adults. However, the abundances of *Bacteroides fragilis*[18], *Clostridium hathewayi*[18], *Eggerthella lenta*[20], *Flavonifractor plautii*[23] and *Ruminococcus gnavus*[24] were significantly increased in frail older adults.

DISCUSSION

This qualitative systematic review, which included 11 eligible studies with 912 older adults over 65 years of age, investigated the relationships between changes in gut microbiota diversity and composition and frailty in older adults. For gut microbiota diversity, the results, which are based on consistent findings reported by more than two eligible studies, revealed a significant decrease in α diversity and a significant increase in β diversity in frail older adults. In terms of the gut microbiota composition, although there was wide variation in the gut microbiota composition reported in the included studies, the consistent results revealed significant differences in the relative abundance of some gut microbiota compositions at different levels, including phylum, family, genus and species, between frail and non-frail older adults. These findings suggest that changes in the gut microbiota may be associated with frailty in older adults.

An increasing number of studies have reported that altered gut microbiota play an important role as a risk factor in the development of many chronic diseases[28-30]. The gut microbiota in healthy individuals maintains a symbiotic relationship with the host but also triggers some pathological processes and causes the evolution of some diseases if potentially pathogenic bacteria overgrow and alter the diversity and abundance of the gut microbiota[31]. The mechanism is related to a deficiency or excess of metabolites resulting from an imbalance in the gut microbiota, which fundamentally affects the physiological status of the host cells and has direct or indirect toxic effects on hormones and the host organism[32]. The gut microbiota is a highly complex and diverse ecosystem of microorganisms living in the digestive tract, and the balance of beneficial and pathogenic bacteria in the gut microbiome is helpful for maintaining host health and homeostasis[33]. However, both environmental factors and host genetics can affect the homeostatic balance of the gut microbiota and lead to a dysbiotic microbiome configuration by altering the diversity and richness of the gut microbiota[34]. Seven studies included in this review compared the differences in gut microbiota diversity between frail and non-frail older adults. Two of the seven studies reported significantly greater β diversity and significantly lower α diversity in frail than non-frail older adults. These findings suggest a possible separation in gut microbiota diversity in older adults with frailty.

The composition of the gut microbiota in older adults can be altered by the constant influence of external environmental factors, such as diet, medication, physical activity, and social environment. Altered gut microbiota composition has also been shown to play an important role in the development of age-related chronic diseases[35]. The gut microbiome can influence host physical function by regulating nutrient absorption, inflammation, oxidative stress, immune function, and anabolic balance and is associated with the progression of aged-physical frailty[35,36]. Among the relative abundances at the phylum level between frail and non-frail older adults, the current review revealed a significant increase in the *Actinobacteria, Proteobacteria, Verrucomicrobia* and *Synergistetes* phyla and a significant decrease in the *Firmicutes* and *Fusobacteria* phyla in frail older adults. These phyla are dominant in healthy humans and are pivotal in the maintenance of gut homeostasis[37,38]. There is evidence of positive associations between increased *Actinobacteria, Proteobacteria, Verrucomicrobia,* and *Synergistetes* phyla and inflammation-related diseases[39,40]. Conversely, the abundance of the *Firmicutes* phylum was negatively associated with inflammatory responses[41].

With respect to the relative abundance of families between frail and non-frail older adults, the current review revealed that the abundances of *Peptostreptococcaceae*, *Bifidobacteriaceae*, *Mogibacteriaceae*, and *Coriobacteriaceae* as well as *Enterobacteriaceae* and *Moraxellaceae* families were greater in frail than in non-frail older adults. Most of them (*Bifidobacteriaceae*, *Mogibacteriaceae, Coriobacteriaceae*, *Enterobacteriaceae X* and *Moraxellaceae*) belong to the *Actinobacteria* or *Proteobacteria* phylum and have previously been implicated in accelerating the aging process through telomere attrition, cellular senescence, inflammasome activation and impaired mitochondrial function, which have been described as correlates of biological aging or are abundant in elderly individuals[42,43]; furthermore, some of them also seem to be positively correlated with various nutritional and physical features[44,45].

With respect to the genera and species levels, more than one study in the current review reported that the abundances of genera (*Roseburia, Faecalibacterium, and Prevotella)* and species *(Faecalibacterium prausnitzii* and *Prevotella copri)* were significantly lower in frail older adults. The *Roseburia* and *Faecalibacterium* genera have anti-inflammatory properties, which are likely mediated by the short-chain fatty acid butyrate[46,47]. *Roseburia* is a anaerobic bacteria that produces butyrate that metabolizes indigestible carbohydrates to produce short-chain fatty acids (particularly high levels of butyric acid), which maintain intestinal function, immune function, and anti-inflammatory properties[47,48]. Furthermore, a lower *Roseburia* level was also found to be associated with inflammation-related diseases such as diabetes, obesity, atherosclerosis, and nonalcoholic liver steatohepatitis[47]. *Faecalibacterium prausnitzii,* which is the only species of the *Faecalibacterium* genus, is a genus of bacteria that produces butyrate and has anti-inflammatory effects[46]. Moreover, the abundance of *Faecalibacterium prausnitzii* is obviously lower in patients with gastrointestinal inflammation and ulcerative colitis (UC)[49]. Hedin *et al*[50] also reported that the abundances of *Faecalibacterium prausnitzii* and *Roseburia* are decreased in patients with the inflammatory Crohn's disease. *Prevotella* and *Prevotella copri*, which belong to the *Prevotellaceae* in this review, were reported to be decreased in frail older adults. *Prevotella* species significantly colonize the human intestine, especially *Prevotella copri,* which is prevalent in populations fed high-fiber diets and is associated with beneficial outcomes, including reduced visceral fat and improved glucose tolerance[51,52]. Studies have shown that *Prevotella copri* transplantation may attenuate oxidative stress and blood-brain barrier damage and alleviate motor and cognitive deficits [53]. In addition, some single studies included in this review reported that the abundances of some genera or species, such as *Eubacterium, Gemella, Lachnoanaerobaculum, Bacteroides vulgatus, Megasphaera, Haemophilus, Adlercreutzia, Clostridium, Coprococcus, and Blautia*, were significantly lower in frail than in non-frail older adults. Most of these microbiomes have been found to be beneficial. For example, several members of the genus *Eubacterium* can produce butyrate, which plays important roles in the immunomodulation and inhibition of inflammation in the gut microbiome[54]. *Eubacterium*, *Gemella*, *Lachnoanaerobaculum* and *Tyzzerella* belong to *Firmicutes,* and an increase in *Firmicutes* is associated with a reduction in inflammatory responses[41]. Moreover, the current review revealed that some genera or species, including *Oscillospira*, *Ruminococcus*, *Alistipes*, *Bacteroides*, *Bacteroides fragilis*, *Pyramidobacter, Eggerthella*, *Olsenella*, *Atopobium, Parabacteroides, etc.,* were more enriched in the frail than the non-frail older adults in the individual included studies; some of these genera or species may be related to the pathological mechanisms of frailty. It has been reported that *Oscillospira* abundance is positively correlated with inflammation in type II diabetes mellitus patients[55] and is associated with a lower body mass index[56]. *Ruminococcus gnavus,* which is a type of Ruminococcus, is enriched in inflammatory diseases, such as inflammatory bowel disease[57]. Treatment of UC patients with fecal microbiome transplants revealed that disease progression was more likely to recrudesce in those who received high concentrations of *Ruminococcus* donors[58]. *Ruminococcus* also aggravated amyotrophic lateral sclerosis in mice, leading to further frailty[59]. *Alistipes, Bacteroides* and *Bacteroides vulgatus* are commonly associated with chronic intestinal inflammation[41,60]. In this review, the results of *Lactobacillus* in the included studies were not consistent, and its relative abundance was greater in the frail older adults in three studies but was lower in the frail older adults in one study. The reason may be related to the different diets of the participants in those studies.

This systematic review provides a comprehensive summary and overview of the current research on the gut microbiota and frailty in adults over 60 years of age. By focusing on older adults over 60 years of age, the frailty states assessed by comprehensive tools, and the non-frail control group consisting mainly of community-dwelling healthy older adults or those with comorbidities, the findings of this review may therefore provide informative guidance for the prevention or rehabilitation of frailty in community-dwelling older adults. However, the following limitations should be acknowledged, as they may affect the interpretation of these findings. First, most of the included studies were cross-sectional in design, which limits the interpretation of the results regarding causality between changes in the gut microbiota and frailty in older adults. Second, the small sample size and insufficient number of studies may hinder the generalization of the findings of this review. The human gut microbiota is complex and may be influenced by internal and external factors. The small number of included studies may limit the ability to observe the influence of confounding factors such as diet, physical activity, comorbid conditions, and medications. In addition, the variation in the measurement of frailty and the gut microbiota across the included studies also makes accurate assessment or analysis of the

associations between the gut microbiota outcomes and frailty difficult.

CONCLUSION

The current review revealed significant changes in the α-diversity and β-diversity and composition of the gut microbiota at the phylum, family, genus, or species level in frail and non-frail older adults aged over 60 years. These changes are commonly reflected by a decrease in the beneficial microbiota (*e.g.*, *Faecalibacterium prausnitzii* at the species level; *Roseburia*, *Eubacterium*, and *Faecalibacterium* at the genus level) and an increase in the pathogenic microbiota (*e.g.*, *Oscillospira*, *Ruminococcus*, *Alistipes*, *Eggerthella*, and *Bacteroides* at the genus level). Future research with large samples and a prospective design is needed to further investigate the impact of specific gut microbiota on frailty in adults over 60 years of age.

FOOTNOTES

Author contributions: Wen NN was responsible for conceptualization, literature screening, data curation, extraction, methodology and writing original draft; Sun LW and Geng Q were responsible for literature screening, data curation, extraction and methodology; Zheng GH was responsible for conceptualization, methodology, project administration, supervision, writing original draft, writing review, and editing; all of the authors read and approved the final version of the manuscript to be published.

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

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: China

ORCID number: Guo-Hua Zheng 0000-0002-4229-7346.

S-Editor: Luo ML
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Walston J**, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, Ershler WB, Harris T, Fried LP. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc* 2006; **54**: 991-1001 [PMID: 16776798 DOI: 10.1111/j.1532-5415.2006.00745.x]
2 **Hoogendijk EO**, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet* 2019; **394**: 1365-1375 [PMID: 31609228 DOI: 10.1016/S0140-6736(19)31786-6]
3 **Collard RM**, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* 2012; **60**: 1487-1492 [PMID: 22881367 DOI: 10.1111/j.1532-5415.2012.04054.x]
4 **Rensa R**, Setiati S, Laksmi PW, Rinaldi I. Factors Associated with Physical Frailty in Elderly Women with Low Socioeconomic Status in Urban Communities: A Cross-Sectional Study. *Acta Med Indones* 2019; **51**: 220-229 [PMID: 31699945]
5 **Xie B**, Ma C, Chen Y, Wang J. Prevalence and risk factors of the co-occurrence of physical frailty and cognitive impairment in Chinese community-dwelling older adults. *Health Soc Care Community* 2021; **29**: 294-303 [PMID: 32657490 DOI: 10.1111/hsc.13092]
6 **Wang X**, Wu M. Research progress of gut microbiota and frailty syndrome. *Open Med (Wars)* 2021; **16**: 1525-1536 [PMID: 34712824 DOI: 10.1515/med-2021-0364]
7 **Rizka A**, Indrarespati A, Dwimartutie N, Muhadi M. Frailty among Older Adults Living in Nursing Homes in Indonesia: Prevalence and Associated Factors. *Ann Geriatr Med Res* 2021; **25**: 93-97 [PMID: 33975423 DOI: 10.4235/agmr.21.0033]
8 **Chen SY**, Wang TY, Zhao C, Wang HJ. Oxidative stress bridges the gut microbiota and the occurrence of frailty syndrome. *World J Gastroenterol* 2022; **28**: 5547-5556 [PMID: 36304085 DOI: 10.3748/wjg.v28.i38.5547]
9 **Jackson MA**, Jeffery IB, Beaumont M, Bell JT, Clark AG, Ley RE, O'Toole PW, Spector TD, Steves CJ. Erratum to: signatures of early frailty in the gut microbiota. *Genome Med* 2016; **8**: 21 [PMID: 26888550 DOI: 10.1186/s13073-016-0275-2]
10 **Meng X**, Zhang G, Cao H, Yu D, Fang X, de Vos WM, Wu H. Gut dysbacteriosis and intestinal disease: mechanism and treatment. *J Appl Microbiol* 2020; **129**: 787-805 [PMID: 32277534 DOI: 10.1111/jam.14661]
11 **Schirmer M**, Garner A, Vlamakis H, Xavier RJ. Microbial genes and pathways in inflammatory bowel disease. *Nat Rev Microbiol* 2019; **17**: 497-511 [PMID: 31249397 DOI: 10.1038/s41579-019-0213-6]

12 **Hogan DB**, Maxwell CJ, Afilalo J, Arora RC, Bagshaw SM, Basran J, Bergman H, Bronskill SE, Carter CA, Dixon E, Hemmelgarn B, Madden K, Mitnitski A, Rolfson D, Stelfox HT, Tam-Tham H, Wunsch H. A Scoping Review of Frailty and Acute Care in Middle-Aged and Older Individuals with Recommendations for Future Research. *Can Geriatr J* 2017; **20**: 22-37 [PMID: 28396706 DOI: 10.5770/cgj.20.240]

13 **Ticinesi A**, Nouvenne A, Cerundolo N, Catania P, Prati B, Tana C, Meschi T. Gut Microbiota, Muscle Mass and Function in Aging: A Focus on Physical Frailty and Sarcopenia. *Nutrients* 2019; **11**: 1633 [PMID: 31319564 DOI: 10.3390/nu11071633]

14 **Stang A**. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]

15 **Chou R**, Baker WL, Bañez LL, Iyer S, Myers ER, Newberry S, Pincock L, Robinson KA, Sardenga L, Sathe N, Springs S, Wilt TJ. Agency for Healthcare Research and Quality Evidence-based Practice Center methods provide guidance on prioritization and selection of harms in systematic reviews. *J Clin Epidemiol* 2018; **98**: 98-104 [PMID: 29409913 DOI: 10.1016/j.jclinepi.2018.01.007]

16 **van Tongeren SP**, Slaets JP, Harmsen HJ, Welling GW. Fecal microbiota composition and frailty. *Appl Environ Microbiol* 2005; **71**: 6438-6442 [PMID: 16204576 DOI: 10.1128/AEM.71.10.6438-6442.2005]

17 **Xu Y**, Wang Y, Li H, Dai Y, Chen D, Wang M, Jiang X, Huang Z, Yu H, Huang J, Xiong Z. Altered Fecal Microbiota Composition in Older Adults With Frailty. *Front Cell Infect Microbiol* 2021; **11**: 696186 [PMID: 34485176 DOI: 10.3389/fcimb.2021.696186]

18 **Lim MY**, Hong S, Kim JH, Nam YD. Association Between Gut Microbiome and Frailty in the Older Adult Population in Korea. *J Gerontol A Biol Sci Med Sci* 2021; **76**: 1362-1368 [PMID: 33437992 DOI: 10.1093/gerona/glaa319]

19 **Picca A**, Ponziani FR, Calvani R, Marini F, Biancolillo A, Coelho-Junior HJ, Gervasoni J, Primiano A, Putignani L, Del Chierico F, Reddel S, Gasbarrini A, Landi F, Bernabei R, Marzetti E. Gut Microbial, Inflammatory and Metabolic Signatures in Older People with Physical Frailty and Sarcopenia: Results from the BIOSPHERE Study. *Nutrients* 2019; **12**: 65 [PMID: 31887978 DOI: 10.3390/nu12010065]

20 **Margiotta E**, Miragoli F, Callegari ML, Vettoretti S, Caldiroli L, Meneghini M, Zanoni F, Messa P. Gut microbiota composition and frailty in elderly patients with Chronic Kidney Disease. *PLoS One* 2020; **15**: e0228530 [PMID: 32236095 DOI: 10.1371/journal.pone.0228530]

21 **Zhang B**, Yu J, Yang Y, Wang Z, Lu S, Chen R, Lu W, Yu Z, Hong K. Relationship between frailty degree and intestinal microbiome in elderly patients with hypertension complicated with type 2 diabetes mellitus in community. *Shiyong Laonian Yixue* 2022; **36**: 663-669 [DOI: 10.3969/j.issn.1003-9198.2022.07.005]

22 **Zhang L**, Liao J, Chen Q, Chen M, Kuang Y, Chen L, He W. Characterization of the gut microbiota in frail elderly patients. *Aging Clin Exp Res* 2020; **32**: 2001-2011 [PMID: 31656031 DOI: 10.1007/s40520-019-01385-2]

23 **Haran JP**, Zeamer A, Ward DV, Dutta P, Bucci V, McCormick BA. The Nursing Home Older Adult Gut Microbiome Composition Shows Time-dependent Dysbiosis and Is Influenced by Medication Exposures, Age, Environment, and Frailty. *J Gerontol A Biol Sci Med Sci* 2021; **76**: 1930-1938 [PMID: 34125200 DOI: 10.1093/gerona/glab167]

24 **Haran JP**, Bucci V, Dutta P, Ward D, McCormick B. The nursing home elder microbiome stability and associations with age, frailty, nutrition and physical location. *J Med Microbiol* 2018; **67**: 40-51 [PMID: 29134939 DOI: 10.1099/jmm.0.000640]

25 **Larson PJ**, Oh J, Robison J, Grady J, Kuchel G. 1206. Association of Aging, Frailty and Place of Residence with Skin, Oral and Gut Microbiome Characteristics and Pathogenicity Reservoirs. *Open Forum Infectious Diseases* 2020; **7**: S625-S625 [DOI: 10.1093/ofid/ofaa439.1391]

26 **Ticinesi A**, Milani C, Lauretani F, Nouvenne A, Mancabelli L, Lugli GA, Turroni F, Duranti S, Mangifesta M, Viappiani A, Ferrario C, Maggio M, Ventura M, Meschi T. Gut microbiota composition is associated with polypharmacy in elderly hospitalized patients. *Sci Rep* 2017; **7**: 11102 [PMID: 28894183 DOI: 10.1038/s41598-017-10734-y]

27 **Kang L**, Li P, Wang D, Wang T, Hao D, Qu X. Alterations in intestinal microbiota diversity, composition, and function in patients with sarcopenia. *Sci Rep* 2021; **11**: 4628 [PMID: 33633246 DOI: 10.1038/s41598-021-84031-0]

28 **Wei W**, Wang S, Xu C, Zhou X, Lian X, He L, Li K. Gut microbiota, pathogenic proteins and neurodegenerative diseases. *Front Microbiol* 2022; **13**: 959856 [PMID: 36466655 DOI: 10.3389/fmicb.2022.959856]

29 **Tiwari P**, Dwivedi R, Bansal M, Tripathi M, Dada R. Role of Gut Microbiota in Neurological Disorders and Its Therapeutic Significance. *J Clin Med* 2023; **12**: 1650 [PMID: 36836185 DOI: 10.3390/jcm12041650]

30 **Katsimichas T**, Theofilis P, Tsioufis K, Tousoulis D. Gut Microbiota and Coronary Artery Disease: Current Therapeutic Perspectives. *Metabolites* 2023; **13**: 256 [PMID: 36837875 DOI: 10.3390/metabo13020256]

31 **Olvera-Rosales LB**, Cruz-Guerrero AE, Ramírez-Moreno E, Quintero-Lira A, Contreras-López E, Jaimez-Ordaz J, Castañeda-Ovando A, Añorve-Morga J, Calderón-Ramos ZG, Arias-Rico J, González-Olivares LG. Impact of the Gut Microbiota Balance on the Health-Disease Relationship: The Importance of Consuming Probiotics and Prebiotics. *Foods* 2021; **10**: 1261 [PMID: 34199351 DOI: 10.3390/foods10061261]

32 **Liu J**, Tan Y, Cheng H, Zhang D, Feng W, Peng C. Functions of Gut Microbiota Metabolites, Current Status and Future Perspectives. *Aging Dis* 2022; **13**: 1106-1126 [PMID: 35855347 DOI: 10.14336/AD.2022.0104]

33 **DAS B**, Nair GB. Homeostasis and dysbiosis of the gut microbiome in health and disease. *J Biosci* 2019; **44**: 117 [PMID: 31719226]

34 **Sommer F**, Anderson JM, Bharti R, Raes J, Rosenstiel P. The resilience of the intestinal microbiota influences health and disease. *Nat Rev Microbiol* 2017; **15**: 630-638 [PMID: 28626231 DOI: 10.1038/nrmicro.2017.58]

35 **Coman V**, Vodnar DC. Gut microbiota and old age: Modulating factors and interventions for healthy longevity. *Exp Gerontol* 2020; **141**: 111095 [PMID: 32979504 DOI: 10.1016/j.exger.2020.111095]

36 **Ni Lochlainn M**, Bowyer RCE, Steves CJ. Dietary Protein and Muscle in Aging People: The Potential Role of the Gut Microbiome. *Nutrients* 2018; **10**: 929 [PMID: 30036990 DOI: 10.3390/nu10070929]

37 **Binda C**, Lopetuso LR, Rizzatti G, Gibiino G, Cennamo V, Gasbarrini A. Actinobacteria: A relevant minority for the maintenance of gut homeostasis. *Dig Liver Dis* 2018; **50**: 421-428 [PMID: 29567414 DOI: 10.1016/j.dld.2018.02.012]

38 **Arumugam M**, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Doré J; MetaHIT Consortium, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. *Nature* 2011; **473**: 174-180 [PMID:

21508958 DOI: 10.1038/nature09944]

39 **Li Z**, Lu G, Li Z, Wu B, Luo E, Qiu X, Guo J, Xia Z, Zheng C, Su Q, Zeng Y, Chan WY, Su X, Cai Q, Xu Y, Chen Y, Wang M, Poon WS, Luo X. Altered Actinobacteria and Firmicutes Phylum Associated Epitopes in Patients With Parkinson's Disease. *Front Immunol* 2021; **12**: 632482 [PMID: 34276644 DOI: 10.3389/fimmu.2021.632482]

40 **Rodriguez-Palacios A**, Cominelli F. Myeloperoxidases and Proteobacteria: Reliable Interspecies Biomarkers to Identify and Monitor Pro-inflammatory Diets in Humans. *Inflamm Bowel Dis* 2019; **25**: e1-e2 [PMID: 29846576 DOI: 10.1093/ibd/izy197]

41 **Samaddar A**, van Nispen J, Armstrong A, Song E, Voigt M, Murali V, Krebs J, Manithody C, Denton C, Ericsson AC, Jain AK. Lower systemic inflammation is associated with gut firmicutes dominance and reduced liver injury in a novel ambulatory model of parenteral nutrition. *Ann Med* 2022; **54**: 1701-1713 [PMID: 35706376 DOI: 10.1080/07853890.2022.2081871]

42 **Boopathi S**, Kumar RMS, Priya PS, Haridevamuthu B, Nayak SPRR, Chulenbayeva L, Almagul K, Arockiaraj J. Gut Enterobacteriaceae and uraemic toxins - Perpetrators for ageing. *Exp Gerontol* 2023; **173**: 112088 [PMID: 36646294 DOI: 10.1016/j.exger.2023.112088]

43 **Clavel T**, Desmarchelier C, Haller D, Gérard P, Rohn S, Lepage P, Daniel H. Intestinal microbiota in metabolic diseases: from bacterial community structure and functions to species of pathophysiological relevance. *Gut Microbes* 2014; **5**: 544-551 [PMID: 25003516 DOI: 10.4161/gmic.29331]

44 **Aleman FDD**, Valenzano DR. Microbiome evolution during host aging. *PLoS Pathog* 2019; **15**: e1007727 [PMID: 31344129 DOI: 10.1371/journal.ppat.1007727]

45 **Rautio M**, Eerola E, Väisänen-Tunkelrott ML, Molitoris D, Lawson P, Collins MD, Jousimies-Somer H. Reclassification of Bacteroides putredinis (Weinberg *et al*., 1937) in a new genus Alistipes gen. nov., as Alistipes putredinis comb. nov., and description of Alistipes finegoldii sp. nov., from human sources. *Syst Appl Microbiol* 2003; **26**: 182-188 [PMID: 12866844 DOI: 10.1078/072320203322346029]

46 **Ferreira-Halder CV**, Faria AVS, Andrade SS. Action and function of Faecalibacterium prausnitzii in health and disease. *Best Pract Res Clin Gastroenterol* 2017; **31**: 643-648 [PMID: 29566907 DOI: 10.1016/j.bpg.2017.09.011]

47 **Tamanai-Shacoori Z**, Smida I, Bousarghin L, Loreal O, Meuric V, Fong SB, Bonnaure-Mallet M, Jolivet-Gougeon A. Roseburia spp.: a marker of health? *Future Microbiol* 2017; **12**: 157-170 [PMID: 28139139 DOI: 10.2217/fmb-2016-0130]

48 **Kasahara K**, Krautkramer KA, Org E, Romano KA, Kerby RL, Vivas EI, Mehrabian M, Denu JM, Bäckhed F, Lusis AJ, Rey FE. Interactions between Roseburia intestinalis and diet modulate atherogenesis in a murine model. *Nat Microbiol* 2018; **3**: 1461-1471 [PMID: 30397344 DOI: 10.1038/s41564-018-0272-x]

49 **Laursen MF**, Laursen RP, Larnkjær A, Mølgaard C, Michaelsen KF, Frøkiær H, Bahl MI, Licht TR. Faecalibacterium Gut Colonization Is Accelerated by Presence of Older Siblings. *mSphere* 2017; **2**: e00448-17 [PMID: 29202044 DOI: 10.1128/mSphere.00448-17]

50 **Hedin CR**, McCarthy NE, Louis P, Farquharson FM, McCartney S, Taylor K, Prescott NJ, Murrells T, Stagg AJ, Whelan K, Lindsay JO. Altered intestinal microbiota and blood T cell phenotype are shared by patients with Crohn's disease and their unaffected siblings. *Gut* 2014; **63**: 1578-1586 [PMID: 24398881 DOI: 10.1136/gutjnl-2013-306226]

51 **Ley RE**. Gut microbiota in 2015: Prevotella in the gut: choose carefully. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 69-70 [PMID: 26828918 DOI: 10.1038/nrgastro.2016.4]

52 **Ahmed HS**. The Impact of Prevotella on Neurobiology in Aging: Deciphering Dendritic Cell Activity and Inflammatory Dynamics. *Mol Neurobiol* 2024; **61**: 9240-9251 [PMID: 38613648 DOI: 10.1007/s12035-024-04156-x]

53 **Gu N**, Yan J, Tang W, Zhang Z, Wang L, Li Z, Wang Y, Zhu Y, Tang S, Zhong J, Cheng C, Sun X, Huang Z. Prevotella copri transplantation promotes neurorehabilitation in a mouse model of traumatic brain injury. *J Neuroinflammation* 2024; **21**: 147 [PMID: 38835057 DOI: 10.1186/s12974-024-03116-5]

54 **Mukherjee A**, Lordan C, Ross RP, Cotter PD. Gut microbes from the phylogenetically diverse genus Eubacterium and their various contributions to gut health. *Gut Microbes* 2020; **12**: 1802866 [PMID: 32835590 DOI: 10.1080/19490976.2020.1802866]

55 **Zhu Y**, Dong L, Huang L, Shi Z, Dong J, Yao Y, Shen R. Effects of oat β-glucan, oat resistant starch, and the whole oat flour on insulin resistance, inflammation, and gut microbiota in high-fat-diet-induced type 2 diabetic rats. *JFF* 2020; **69**: 103939 [DOI: 10.1016/j.jff.2020.103939]

56 **Tims S**, Derom C, Jonkers DM, Vlietinck R, Saris WH, Kleerebezem M, de Vos WM, Zoetendal EG. Microbiota conservation and BMI signatures in adult monozygotic twins. *ISME J* 2013; **7**: 707-717 [PMID: 23190729 DOI: 10.1038/ismej.2012.146]

57 **Hall AB**, Yassour M, Sauk J, Garner A, Jiang X, Arthur T, Lagoudas GK, Vatanen T, Fornelos N, Wilson R, Bertha M, Cohen M, Garber J, Khalili H, Gevers D, Ananthakrishnan AN, Kugathasan S, Lander ES, Blainey P, Vlamakis H, Xavier RJ, Huttenhower C. A novel Ruminococcus gnavus clade enriched in inflammatory bowel disease patients. *Genome Med* 2017; **9**: 103 [PMID: 29183332 DOI: 10.1186/s13073-017-0490-5]

58 **Fuentes S**, Rossen NG, van der Spek MJ, Hartman JH, Huuskonen L, Korpela K, Salojärvi J, Aalvink S, de Vos WM, D'Haens GR, Zoetendal EG, Ponsioen CY. Microbial shifts and signatures of long-term remission in ulcerative colitis after faecal microbiota transplantation. *ISME J* 2017; **11**: 1877-1889 [PMID: 28398347 DOI: 10.1038/ismej.2017.44]

59 **Blacher E**, Bashiardes S, Shapiro H, Rothschild D, Mor U, Dori-Bachash M, Kleimeyer C, Moresi C, Harnik Y, Zur M, Zabari M, Brik RB, Kviatcovsky D, Zmora N, Cohen Y, Bar N, Levi I, Amar N, Mehlman T, Brandis A, Biton I, Kuperman Y, Tsoory M, Alfahel L, Harmelin A, Schwartz M, Israelson A, Arike L, Johansson MEV, Hansson GC, Gotkine M, Segal E, Elinav E. Potential roles of gut microbiome and metabolites in modulating ALS in mice. *Nature* 2019; **572**: 474-480 [PMID: 31330533 DOI: 10.1038/s41586-019-1443-5]

60 **Parker BJ**, Wearsch PA, Veloo ACM, Rodriguez-Palacios A. The Genus Alistipes: Gut Bacteria With Emerging Implications to Inflammation, Cancer, and Mental Health. *Front Immunol* 2020; **11**: 906 [PMID: 32582143 DOI: 10.3389/fimmu.2020.00906]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6826-6833

DOI: 10.12998/wjcc.v12.i35.6826

ISSN 2307-8960 (online)

CASE REPORT

psk1 virulence gene-induced pulmonary and systemic tuberculosis in a young woman with normal immune function: A case report

Fan Wu, Bin Yang, Yan Xiao, Li-Li Ren, Hong-Yi Chen, Xin-Lan Hu, Yan-Yu Pan, Yu-Sheng Chen, Hong-Ru Li

Specialty type: Infectious diseases

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

P-Reviewer: Conteduca G

Received: January 2, 2024
Revised: July 2, 2024
Accepted: July 23, 2024
Published online: December 16, 2024
Processing time: 295 Days and 18 Hours

Fan Wu, Yu-Sheng Chen, Department of Respiratory and Critical Care Medicine, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou 350001, Fujian Province, China

Bin Yang, Yan Xiao, Li-Li Ren, NHC Key Laboratory of Systems Biology of Pathogens and Christophe Mérieux Laboratory, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Hong-Yi Chen, Emergency Department, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou 350001, Fujian Province, China

Xin-Lan Hu, Clinical Microbiology Laboratory, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou 350001, Fujian Province, China

Yan-Yu Pan, Infection Department, The 900th Hospital of the PLA Joint Support Force, Fuzhou 350001, Fujian Province, China

Hong-Ru Li, Department of Infectious Diseases, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou 350001, Fujian Province, China

Corresponding author: Hong-Ru Li, MD, PhD, Chief Doctor, Professor, Department of Infectious Diseases, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, No. 134 East Street, Fuzhou 350001, Fujian Province, China. muzi131122@163.com

Abstract

BACKGROUND

Tuberculosis is a chronic infectious disease and an important public health problem. Despite progress in controlling tuberculosis, the incidence of tuberculosis in China is still very high, with 895000 new cases annually. This case report describes the investigation of a case of severe disseminated tuberculosis in a young adult with normal immune function, conducted to ascertain why a *Mycobacterium tuberculosis* (*M. tuberculosis*) strain caused such severe disease.

CASE SUMMARY

A previously healthy 28-year-old woman presented to our hospital with a 1-mo-

nth history of fever and fatigue. She was diagnosed with severe disseminated pulmonary tuberculosis, spinal tuberculosis with paravertebral abscesses, and tuberculous meningitis. *M. tuberculosis* was isolated from bronchoalveolar lavage fluid. She was treated with standard antituberculous therapy and underwent debridement, bone graft, and internal fixation surgery for spinal tuberculosis. She responded to therapy and regained her ability to walk following the surgery. We analysed the whole-genome sequence of the strain and designated it BLM-A21. Additional *M. tuberculosis* genomes were selected from the Virulence Factor Database (http://www.mgc.ac.cn/cgi-bin/VFs/genus.cgi?Genus=Mycobacterium) for comparison. An evolutionary tree of the BLM-A21 strain was built using PhyML maximum likelihood software. Further gene analysis revealed that, except for the *pks1* gene, BLM-A21 had similar virulence genes to the CDC 1551 and H37Rv strains, which have lower dissemination.

CONCLUSION

We speculate that the *pks1* virulence gene in BLM-A21 may be the key virulence gene responsible for the widespread dissemination of *M. tuberculosis* infection in this previously healthy adult with normal immune function.

Key Words: *Mycobacterium tuberculosis*; Disseminated tuberculosis; Spinal tuberculosis; Tuberculous meningitis; Virulence gene; Whole-genome sequencing; Case report

Core Tip: Tuberculosis is an important public health problem that threatens human health that primarily infects the lungs. We report a case of invasive pulmonary tuberculosis in a young woman with normal immune function. Comparison of the genetic characteristics of the patient's strain with those of other disease-causing strains suggests that its virulence and wide dissemination was attributable to the presence of the *pks1* gene, a genotype that can cause meningitis.

Citation: Wu F, Yang B, Xiao Y, Ren LL, Chen HY, Hu XL, Pan YY, Chen YS, Li HR. *psk1* virulence gene-induced pulmonary and systemic tuberculosis in a young woman with normal immune function: A case report. *World J Clin Cases* 2024; 12(35): 6826-6833
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6826.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6826

INTRODUCTION

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and is an important public health problem. In 1979, China carried out the first national tuberculosis epidemiological survey, which showed that the prevalence of active tuberculosis was 717/100000[1]. Under the modern tuberculosis control and tuberculosis containment strategy implemented by China in 1992, the prevalence was reduced to 59/100000 by 2020[2]. This was mainly due to active prevention, including vaccination with the bacillus Calmette–Guérin (BCG) vaccine. Despite these achievements, China still has one of the highest burdens of tuberculosis worldwide, with 895000 new cases annually[2].

We report a rare case of disseminated pulmonary tuberculosis with secondary systemic hematogenous dissemination in a young woman with normal immune function and no underlying diseases and discuss the possible underlying causes.

CASE PRESENTATION

Chief complaints

A 28-year-old woman presented with a 1-month history of recurrent fever and lower back pain and a 1-week history of dyspnoea.

History of present illness

The patient had been healthy until the onset of the illness 1 month previously. She was admitted to Fujian Provincial Hospital in August 2021.

History of past illness

None.

Personal and family history

She had no known underlying diseases or family history of hereditary diseases. Her parents and sister did not have similar symptoms. She had not been vaccinated with BCG, although her younger sister had received a BCG vaccination.

Physical examination

On admission her vital signs were as follows: Body temperature, 38.8 ℃; pulse rate, 117 beats/minute; respiratory rate, 40 breaths/minute; blood pressure, 127/64 mmHg; and peripheral oxygen saturation, 80% with an inhaled oxygen concentration of 29%. She had shallow, rapid breathing. Chest auscultation revealed bilateral diffuse moist rales. A lump measuring approximately 3.5 cm × 5.0 cm was present in her lumbosacral region, with slight tenderness, poor mobility, and no redness, swelling, or ulceration of the overlying skin.

Laboratory examinations

Her arterial blood gas results with 29% oxygen supplementation were as follows: PH, 7.483; PCO_2, 34.6 mmHg; PO_2, 44.2 mmHg; and the oxygenation index was 152 mmHg. Haematology revealed a white blood cell count of 5100 cells/μL, with 63.6% segmented neutrophils; a haemoglobin level of 131 g/L; and a platelet count of 273000/μL. Blood biochemistry and immunology revealed the following: Serum albumin, 38 g/L; aspartate aminotransferase, 42 U/L; alkaline phosphatase, 110.6 U/L; lactate dehydrogenase, 548 U/L; procalcitonin, 2.4 ng/mL; C-reactive protein, 67.1 mg/L; and erythrocyte sedimentation rate, 13 mm/h. Immune function tests revealed the following: CD3 cell count, 106 cells/μL; CD4 cell count, 58 cells/μL; CD8 cell count, 43 cells/μL; NK cell count, 35 cells/μL; CD19 cell count, 86 cells/μL; CD45 cell count, 227 cells/μL; serum immunoglobulin G, 9.91 g/L; immunoglobulin A, 2.02 g/L; immunoglobulin M, 0.48 g/L; immunoglobulin E, 165 g/L; complement C3, 0.997 g/L; and complement C4, 0.125 g/L. The antinuclear antibody profile (full set of autoimmunity), antineutrophil cytoplasmic antibody, rheumatoid factor, and anticyclic citrulline polypeptide antibody tests were negative. Hepatitis B antibody, human immunodeficiency virus antibody, and syphilis-specific antibody tests were also negative. Sputum bacterial and fungal cultures were negative.

Imaging examinations

Chest computed tomography showed diffuse lesions in both lungs, bone destruction from the eighth thoracic vertebra to the first lumbar vertebra, and a paravertebral soft tissue mass (Figure 1A and B). Enhanced magnetic resonance imaging (MRI) of the thoracolumbar spine showed abnormal signal shadows from the ninth thoracic vertebral body to the 1st lumbar vertebral body and the surrounding soft tissue (Figure 1C-E). Brain enhanced MRI showed abnormal signals in the right parietal lobe (Figure 1F).

MULTIDISCIPLINARY EXPERT CONSULTATION

Further diagnostic workup

The patient underwent immediate endotracheal intubation and bronchoscopy. A bronchoalveolar lavage fluid (BALF) smear was positive for acid-fast bacilli, and a Gene X-pert MTB/RIF assay was positive for *M. tuberculosis* DNA. Next-generation sequencing of blood and BALF, and BALF culture confirmed *M. tuberculosis* infection.

To ascertain why this *M. tuberculosis* strain had caused such a severe infection in a young adult with normal immune function, we analysed the strain using whole-genome sequencing. We designated the strain, which had a total of 4155 genes, BLM-A21. We selected other *M. tuberculosis* genomes from the virulence factor database (VFDB) (http://www.mgc.ac.cn/cgi-bin/VFs/genus.cgi?Genus=Mycobacterium) [3], developed by the bioinformatics research team of the institute of Pathogenic Biology, Chinese Academy of Medical Science. We then performed phylogenetic analysis using PhyML maximum likelihood software[4] to build an evolutionary tree (Figure 2). We found that BLM-A21 had a close evolutionary relationship to CCDC5079, CCDC5180, and Beijing NTR203. Therefore, we analysed the whole genomes of several strains, including CCDC5079, CCDC5180, Beijing NTR203, CDC1551, and classic H37Rv and H37Ra, for subsequent genome comparison, as these strains have previously shown strong dissemination ability[5,6]. We used the BLASTP performance comparison algorithm[7] and the virulence factor protein reference sequence of the VFDB to annotate genes of these species (covering reference genes ≥ 85%, similarity ≥ 80%), and mapped the virulence gene classification and genome position information using CGView[8] (Figure 3). We identified high-virulence genes in BLM-A21 which we displayed in a heat map (Figure 4). Compared with the high-dissemination strains HN878 and W4 of the W/Beijing strain series, CDC 1551 has lower dissemination ability owing to the absence of the genes *pks1–15*. In our study, we found that BLM-A21 had similar virulence genes to CDC 1551 and H37Rv, except for the *pks1* gene, and thus hypothesized that *pks1* was the key virulence gene responsible for the widespread dissemination of the BLM-A21 strain of *M. tuberculosis* in this patient.

FINAL DIAGNOSIS

The patient was diagnosed with severe pulmonary tuberculosis and secondary systemic disseminated tuberculosis, including spinal tuberculosis with a paravertebral abscess, and tuberculous meningitis.

TREATMENT

After receiving isoniazid, rifampicin, ethambutol, and pyrazinamide, the patient's temperature dropped; her cough and

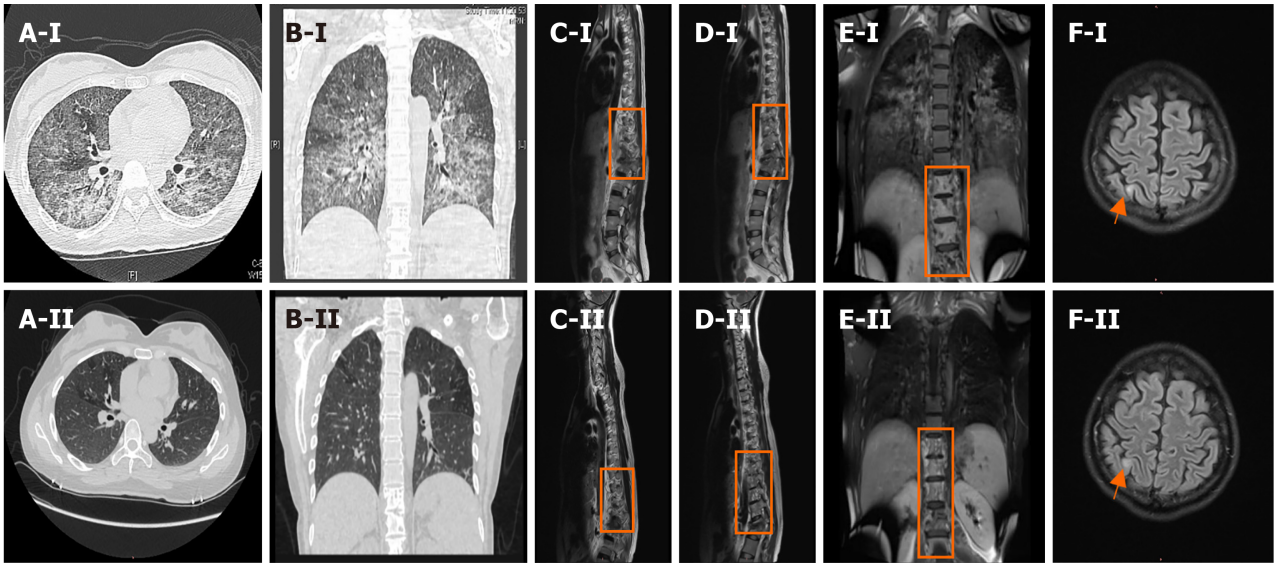

Figure 1 Chest computed tomography and enhanced magnetic resonance imaging of the thoracolumbar spine and brain. A-I and B-I: Chest computed tomography scans showing diffuse lesions in both lungs on admission; C-I, D-I, and E-I: Enhanced magnetic resonance imaging (MRI) of the thoracolumbar spine performed on day 13, showing abnormal signal shadows from the ninth thoracic vertebral body to the first lumbar vertebral body and the surrounding soft tissues; F-I: Enhanced MRI of the brain performed on day 12, showing an abnormal right parietal lobe signal. A-II and B-II: The chest computed tomography scan performed 6 ½ months after admission, showing an improvement in the diffuse lesions in both lungs. C-II, D-II, and E-II: Enhanced MRI of the thoracic spine performed 6 ½ months after admission, showing improved signal shadows from the ninth thoracic vertebral body to the first lumbar vertebral body and the surrounding soft tissues; F-II: Enhanced MRI of the brain performed 6 ½ months after admission, showing similar signal intensities in the right parietal lobe and the frontal lobe.

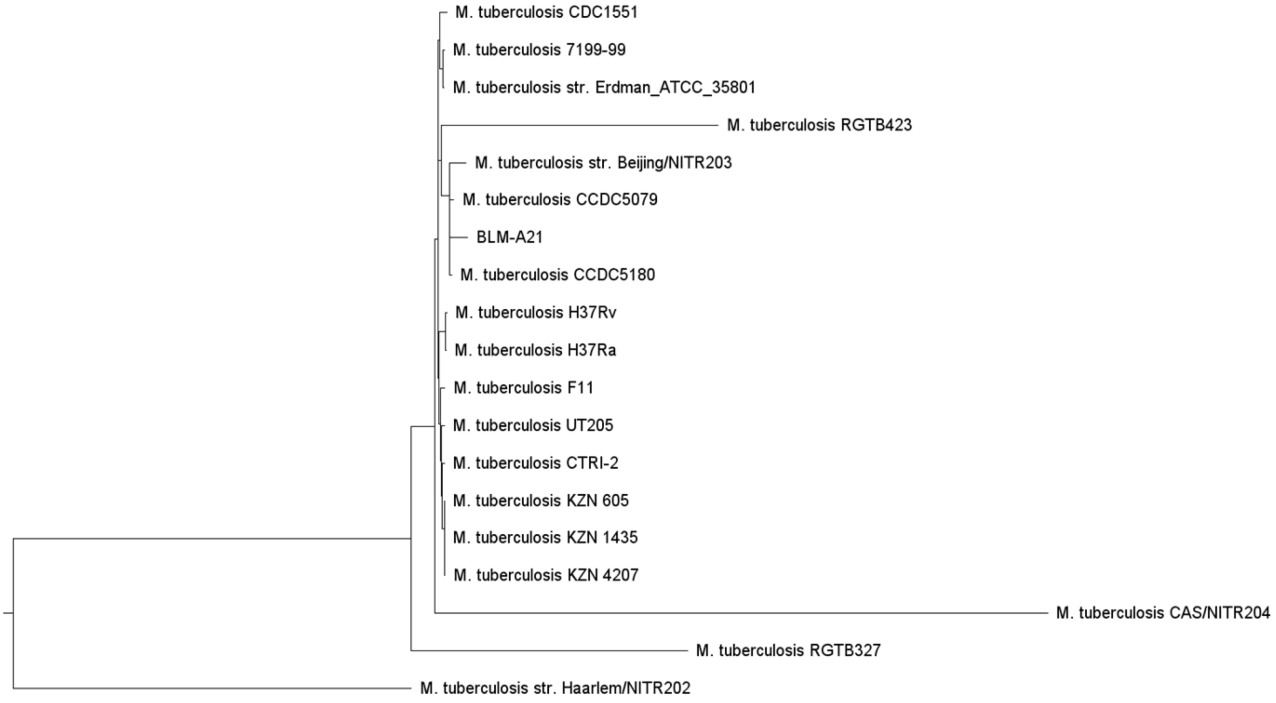

Figure 2 Whole-genome evolutionary tree of *Mycobacterium tuberculosis*. Additional *Mycobacterium tuberculosis* genomes were selected from the Virulence Factor Database (VFDB) (http://www.mgc.ac.cn/cgi-bin/VFs/genus.cgi?Genus=Mycobacterium), developed by the bioinformatics research team of the Institute of Pathogenic Biology, Chinese Academy of Medical Science, and a phylogenetic tree was built using the PhyML (maximum likelihood) software. The whole genomes of several strains, including CCDC5079, CCDC5180, Beijing NTR203, CDC1551, and classic H37Rv and H37Ra, were analysed for subsequent genome comparison, as these strains have previously shown strong dissemination ability. The patient's strain (BLM-A21) was closer to CCDC5079, CCDC5180, and Beijing NTR203 as shown on the evolutionary tree.

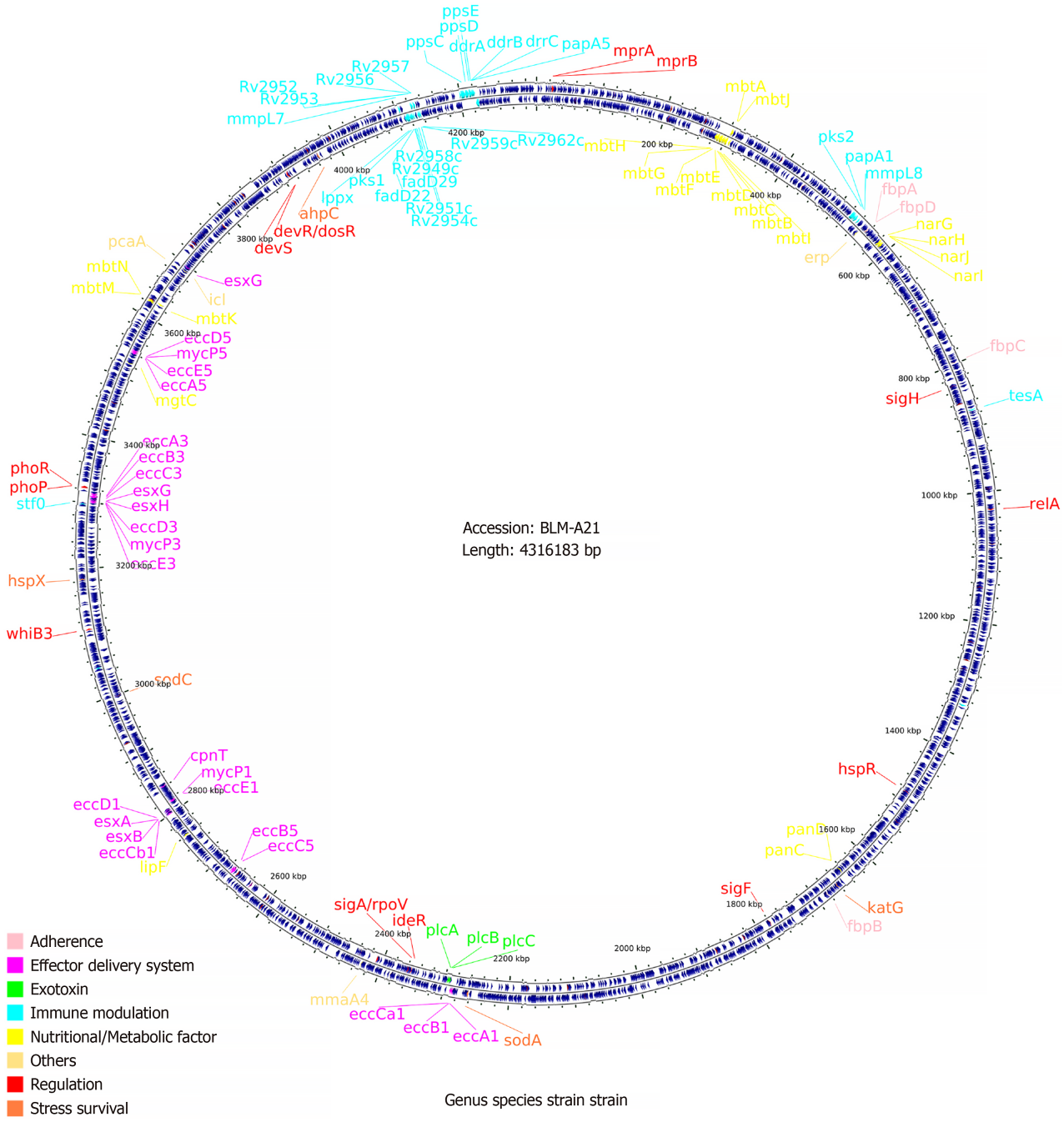

Figure 3 Chromosome genome circle map and virulence factor annotation of *Mycobacterium tuberculosis* strain BLM-A21. The BLASTP performance comparison algorithm and the virulence factor protein reference sequence of the Virulence Factor Database was used to annotate genes of these species, and the virulence gene classification and genome position information was mapped using CGView.

shortness of breath improved, and the tracheal intubation was removed. Imaging of the patient's brain, chest, and vertebral body performed 6 months after starting treatment showed that her condition had greatly improved (Figure 1A-F). Eight months after starting antituberculous treatment, the patient underwent debridement, bone graft, and internal fixation surgery for spinal tuberculosis, and left psoas abscess debridement.

OUTCOME AND FOLLOW-UP

After the surgery the patient has recovered the ability to walk unaided. Pain was evaluated using a visual analogue scale (VAS), with pain intensity graded on a scale of 0 (no pain) to 10 (most severe pain). The Oswestry Disability Index (ODI), which consists of 10 questions with a total score of 100 points, was used to evaluate the degree of lumbar functional impairment. A higher score indicates more severe the functional impairment. Both the VAS and ODI improved markedly after treatment. The VAS and ODI results before, and 6 ½ months after, treatment are shown in Table 1.

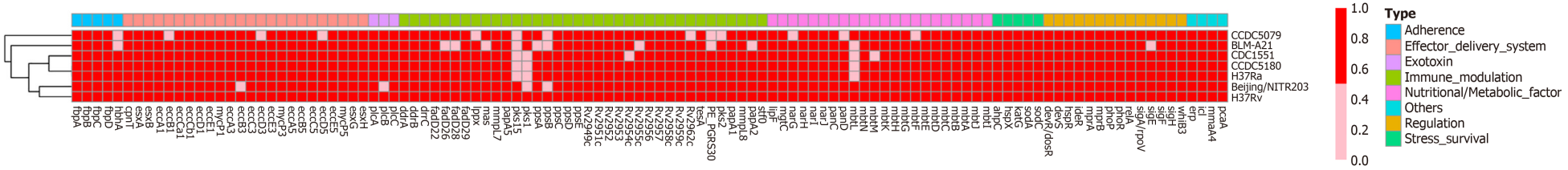

Figure 4 Virulence genes of *Mycobacterium tuberculosis* strains and their related genomes. The red color indicates that the presence of the virulence gene, whereas the pink color indicates the absence of the virulence gene in the genome. As the figure shows, CDC1551 Lacks genes *pks1–15*. BLM-A21 carries the *pks1* gene but lacks *pks15*; nevertheless, the number of other virulence genes is essentially consistent with that of CDC1551 and H37Rv.

DISCUSSION

BCG is an attenuated form of *Mycobacterium bovis* that provides immune protection and has been the only vaccine available against tuberculosis in China since the 1930s. In 2000, the BCG vaccination coverage in newborns reached 90%, effectively preventing miliary tuberculosis and tuberculous meningitis in children, and reducing the risk of *M. tuberculosis* infection in adults[9]. The patient, who had not received BCG vaccination suffered from severe *M. tuberculosis* infection, whereas her sister, who had received BCG vaccination, did not become ill.

Previous studies have shown that most children with hematogenous disseminated pulmonary tuberculosis had not received BCG vaccination[10], suggesting that the risk of severe tuberculosis is higher in individuals without BCG vaccination.

Severe pulmonary tuberculosis is very rare, accounting for approximately 3%-7% of cases[11]. Most patients with severe tuberculosis have had previous contact with an individual with tuberculosis, have weakened cellular immune function, or have other conditions such as anaemia, malnutrition, and a delay in seeking medical treatment[12-15]. However, this patient had none of these predisposing factors. Therefore, we hypothesised that the *pks1* virulence gene of BLM-A21 may have been the reason for the severity of the patient's disease.

A previous study showed that, compared with strains with a high risk of dissemination, strains that lack *pks1–15*, a phenol glycolipid (PGL)-related synthesis gene, have weak ability to disseminate to the central nervous system[16]. We found that BLM-A21 carried the *pks1* gene, but lacked the *pks15* gene, whereas the number of other virulence genes was consistent with that of other low-dissemination strains such as CDC 1551 and H37Rv. Based on an *in vitro* live bacterial transcriptome experiment, *pks1* has been reported to have a greater effect than *pks15* on regulating *fadD22*, *Rv2949c*, *lppX*, *fadD29*, and other genes, thus promoting PGL synthesis. PGL is related to several cell functions, particularly the impermeability of the cell wall, phagocytosis, the defence mechanism against nitroso compounds, oxidative stress, and the ability of mycobacteria to form biofilms, allowing strains to grow rapidly and invade the host[17].

CONCLUSION

We hypothesize that the *pks1* virulence gene of the BLM-A21 *M. tuberculosis* strain, induced severe pulmonary tuberculosis and secondary systemic disseminated tuberculosis in this unvaccinated patient with normal immune function. The mechanism whereby the *pks1* gene causes highly invasive tuberculosis needs further study.

Table 1 The visual analogue scale and Oswestry Disability Index results before, and 6 ½ months after, treatment

	Before treatment	6 ½ months after treatment
VAS score	6	1
ODI score	44	12

VAS: Visual analogue scale; ODI: Oswestry Disability Index.

ACKNOWLEDGEMENTS

We thank the patient for her permission to publish this report, cooperation in drafting the final manuscript, and permission to use images.

FOOTNOTES

Author contributions: Wu F, Yang B, Xiao Y, and Chen H contributed to conceptualisation, supervision, evaluation, and manuscript writing and editing; Yang B, Hu X, and Pan Y contributed to methodology; Ren L, Chen Y, and Li H contributed to manuscript writing and editing; All authors have read and approved the final manuscript.

Supported by the Research on Intelligent Recommendation Decision Model of Geriatrics Based on Big Data, No. 2021CX01010136.

Informed consent statement: The patient provided written informed consent to publish this case study and accompanying images.

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

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: China

ORCID number: Hong-Ru Li 0009-0007-1618-2055.

S-Editor: Liu JH
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Tu DH**. [Tuberculosis control in China for 60 years]. *Zhonghua Jiehe He Huxi Zazhi* 2013; **36**: 886-887 [DOI: 10.3760/cma.j.issn.1001-0939.2013.12.003]
2 **World Health Organization**. Global tuberculosis report 2017. Geneva: World Health Organization; 2017. Available from: https://www.who.int/publications/i/item/9789241565516
3 **Liu B**, Zheng D, Jin Q, Chen L, Yang J. VFDB 2019: a comparative pathogenomic platform with an interactive web interface. *Nucleic Acids Res* 2019; **47**: D687-D692 [PMID: 30395255 DOI: 10.1093/nar/gky1080]
4 **Guindon S**, Delsuc F, Dufayard JF, Gascuel O. Estimating maximum likelihood phylogenies with PhyML. *Methods Mol Biol* 2009; **537**: 113-137 [PMID: 19378142 DOI: 10.1007/978-1-59745-251-9_6]
5 **Kohli S**, Singh Y, Sharma K, Mittal A, Ehtesham NZ, Hasnain SE. Comparative genomic and proteomic analyses of PE/PPE multigene family of Mycobacterium tuberculosis H_{37}Rv and H_{37}Ra reveal novel and interesting differences with implications in virulence. *Nucleic Acids Res* 2012; **40**: 7113-7122 [PMID: 22618876 DOI: 10.1093/nar/gks465]
6 **Bucsan AN**, Rout N, Foreman TW, Khader SA, Rengarajan J, Kaushal D. Mucosal-activated invariant T cells do not exhibit significant lung recruitment and proliferation profiles in macaques in response to infection with Mycobacterium tuberculosis CDC1551. *Tuberculosis (Edinb)* 2019; **116S**: S11-S18 [PMID: 31072689 DOI: 10.1016/j.tube.2019.04.006]
7 **Camacho C**, Coulouris G, Avagyan V, Ma N, Papadopoulos J, Bealer K, Madden TL. BLAST+: architecture and applications. *BMC Bioinformatics* 2009; **10**: 421 [PMID: 20003500 DOI: 10.1186/1471-2105-10-421]
8 **Stothard P**, Grant JR, Van Domselaar G. Visualizing and comparing circular genomes using the CGView family of tools. *Brief Bioinform* 2019; **20**: 1576-1582 [PMID: 28968859 DOI: 10.1093/bib/bbx081]
9 **Zhu BD**, Wang HH. [History and current status of tuberculosis vaccine research]. *Zhonghua Jiehe He Huxi Zazhi* 2007; **30**: 378-382

10 **Yang M**, Yuan P, Wang Y, Chen L, Shi ZY, Luo DX, Huang XQ. [Analysis of clinical prevalence of 502 cases of hematogenous disseminated pulmonary tuberculosis in Sichuan]. *Sichuan Yixue* 2018; **39**: 977-982

11 **Liu TL**. [Practical tuberculosis]. Shenyang: Liaoning Science and Technology Press; 1987; 284-289

12 **Yun J**, Wang AM. [Clinical characteristics of 146 patients with hematogenous disseminated pulmonary tuberculosis and analysis of influencing factors of curative effect]. *Zhongguo Bingan* 2016; **17**: 70-73

13 **Liu XN**, Li Y. [Analysis of clinical characteristics and risk factors of young patients with severe pulmonary tuberculosis]. *Linchuang Feike Zazhi* 2020; **25**: 1419-1423

14 **Ashenafi S**, Bekele A, Aseffa G, Amogne W, Kassa E, Aderaye G, Worku A, Bergman P, Brighenti S. Anemia Is a Strong Predictor of Wasting, Disease Severity, and Progression, in Clinical Tuberculosis (TB). *Nutrients* 2022; **14** [PMID: 36014824 DOI: 10.3390/nu14163318]

15 **Tedla K**, Medhin G, Berhe G, Mulugeta A, Berhe N. Delay in treatment initiation and its association with clinical severity and infectiousness among new adult pulmonary tuberculosis patients in Tigray, northern Ethiopia. *BMC Infect Dis* 2020; **20**: 456 [PMID: 32600284 DOI: 10.1186/s12879-020-05191-4]

16 **Tsenova L**, Ellison E, Harbacheuski R, Moreira AL, Kurepina N, Reed MB, Mathema B, Barry CE 3rd, Kaplan G. Virulence of selected Mycobacterium tuberculosis clinical isolates in the rabbit model of meningitis is dependent on phenolic glycolipid produced by the bacilli. *J Infect Dis* 2005; **192**: 98-106 [PMID: 15942899 DOI: 10.1086/430614]

17 **Ramos B**, Gordon SV, Cunha MV. Revisiting the expression signature of pks15/1 unveils regulatory patterns controlling phenolphtiocerol and phenolglycolipid production in pathogenic mycobacteria. *PLoS One* 2020; **15**: e0229700 [PMID: 32379829 DOI: 10.1371/journal.pone.0229700]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6834-6839

DOI: 10.12998/wjcc.v12.i35.6834

ISSN 2307-8960 (online)

CASE REPORT

Rare primary gastric peripheral T-cell lymphoma not otherwise specified: A case report

Hee Ryeong Jang, Kyungyul Lee, Kyu-Hyoung Lim

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 B

Creativity or Innovation: Grade B

Scientific Significance: Grade C

P-Reviewer: Liu YQ

Received: June 21, 2024

Revised: August 21, 2024

Accepted: September 13, 2024

Published online: December 16, 2024

Processing time: 125 Days and 7.5 Hours

Hee Ryeong Jang, Kyu-Hyoung Lim, Division of Hematology and Oncology, Department of Internal Medicine, Kangwon National University Hospital, Kangwon National University College of Medicine, South Korea

Kyungyul Lee, Department of Pathology, Pathology Center, Seegene Medical Foundation, Seoul 61743, South Korea

Corresponding author: Kyu-Hyoung Lim, MD, PhD, Professor, Division of Hematology and Oncology, Department of Internal Medicine, Kangwon National University Hospital, Kangwon National University College of Medicine, 156 Baengnyeong-ro, Chuncheon 24341, South Korea. kyuhyoung.lim@kangwon.ac.kr

Abstract

BACKGROUND

Gastrointestinal lymphoma typically arises in the stomach, small bowel, or colorectum and is usually a B-cell lymphoma. However, primary T-cell lymphomas originating in the stomach are particularly rare. Gastric peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) is an extremely rare subtype.

CASE SUMMARY

We report a 63-year-old male presenting with epigastric pain. Esophagogastroduodenoscopy revealed a large ulcerative lesion in the gastric cardia. Biopsy and immunohistochemical profiling confirmed PTCL-NOS. Imaging indicated stage II disease involving the stomach and intra-abdominal lymph nodes. The patient is planned to undergo cyclophosphamide, doxorubicin, vincristine, and prednisone or cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide chemotherapy.

CONCLUSION

This case highlights the necessity of considering PTCL-NOS in differential diagnoses of gastric lesions. Comprehensive histopathological and immunohistochemical analysis is crucial for accurate diagnosis and guiding treatment.

Key Words: Gastrointestinal lymphoma; Stomach; Peripheral T-cell lymphoma-not otherwise specified; Extranodal lymphoma; Case report

Core Tip: Gastrointestinal lymphoma is an extranodal malignancy primarily arising in the stomach, small intestine, or colorectum, most commonly presenting as B-cell lymphoma. In contrast, primary T-cell lymphomas of the stomach are exceedingly rare, particularly within the spectrum of T-cell lymphoma subtypes. Among these, gastric peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) is extremely rare. In this report, we present a rare case of a 63-year-old male diagnosed with gastric PTCL-NOS, along with a detailed examination of the clinicopathological features.

Citation: Jang HR, Lee K, Lim KH. Rare primary gastric peripheral T-cell lymphoma not otherwise specified: A case report. *World J Clin Cases* 2024; 12(35): 6834-6839
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6834.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6834

INTRODUCTION

Gastrointestinal (GI) lymphoma is the most common extranodular lymphoma, accounting for 30%-40% of all extranodular lymphoma, and has distinct clinical and pathological characteristics[1,2]. More than 80% of the GI lymphomas are B-cell lymphomas. The stomach is the most commonly affected site for GI lymphoma, followed by the small bowel, colorectum, and esophagus[3,4]. The majority of primary gastric lymphoma cases are B-cell lymphomas, while T-cell lymphomas are known to be rare. The incidence of primary gastric T-cell lymphoma (PG-TCL) is estimated to be exceptionally low, making it challenging to determine, and it is reported through documented cases[3]. Consequently, only a few cases have been reported. The T-cell lymphoma of the stomach is mainly categorized into anaplastic large cell lymphoma (ALCL), natural killer (NK)/T-cell lymphoma, or enteropathy-associated T-cell lymphoma (EATL)[5,6]. Peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) includes all T-cell lymphomas that don't meet the diagnostic criteria of any category.

To the best of our knowledge, primary gastric PTCL-NOS have been rarely reported. Therefore, we present a gastric PTCL-NOS case and describe its clinic-pathological and endoscopic features.

CASE PRESENTATION

Chief complaints

A 63-year-old male was admitted to Kangwon National University Hospital with a 3-week history of epigastric pain.

History of present illness

The patient denied weight loss and febrile sense. Physical examination revealed that his abdomen was soft without tenderness or rebound tenderness.

History of past illness

The patient denied any significant past medical history.

Personal and family history

The patient's personal and family history had no notable findings.

Physical examination

The physical examination revealed that the patient's abdomen was soft. It was not tender. Rebound tenderness was not observed.

Laboratory examinations

Blood test results revealed that white blood cell count, hemoglobin, and platelet count were within normal ranges. However, lactate dehydrogenase level was slightly elevated at 244 U/L (reference range: 119-229 U/L).

In hematoxylin and eosin staining of the stomach tissue, majority of malignant cells were intermediate to large-sized abnormal lymphoid cells. Characteristics commonly found in gastric carcinomas, such as intestinal dysplasia, cylindrical epithelial cells, and prominent intracytoplasmic mucin vacuoles, were not detected in this case. A pan-cytokeratin immunohistochemistry (IHC) test yielded a negative result, ruling out gastric carcinoma. Tests for CD20, PAX5, CD10, and Bcl-6 also returned negative results, excluding the possibility of B-cell lineage lymphoma. CD3, CD5, CD7, and CD4 were expressed positively (Figure 1). These cells also exhibited a relatively elevated Ki-67 proliferation index (30%). The T-cell receptor gamma gene rearrangement test demonstrated a positive result. Pathological findings were indicative of high-grade T-cell lymphoma. Further IHC tests were conducted to differentiate between various subtypes of T-cell lymphoma, including NK/T-cell lymphoma, EATL, monomorphic epitheliotropic intestinal T-cell lymphoma, angioimmunoblastic T-cell lymphoma, ALCL, and PTCL-NOS. However, CD30, ALK (D5F3), CD56, granzyme B, and Epstein-

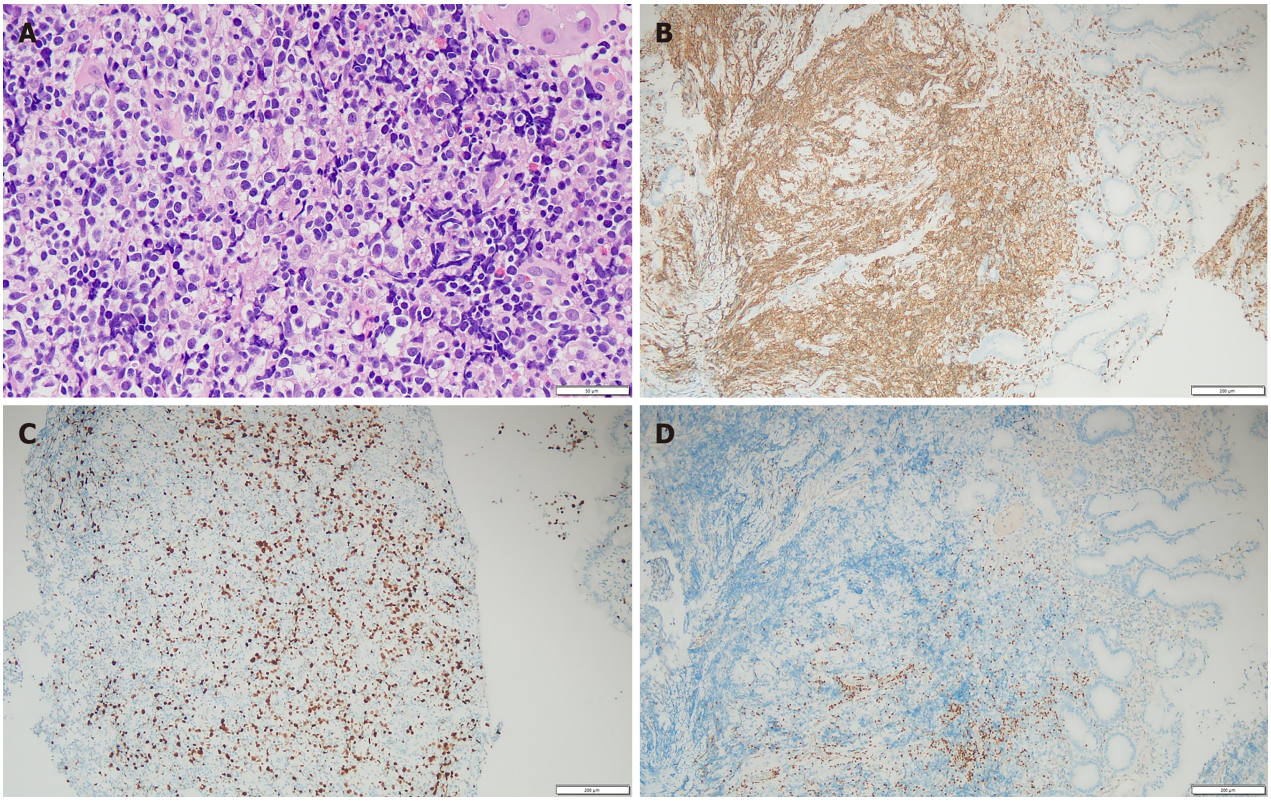

Figure 1 Histopathological findings. A: Hematoxylin and eosin staining of stomach of magnification of 400 ×; B-D: Results of immunohistochemistry revealing the tumor was CD3 positive, Ki-67 positive, and PAX positive (magnification 100 ×).

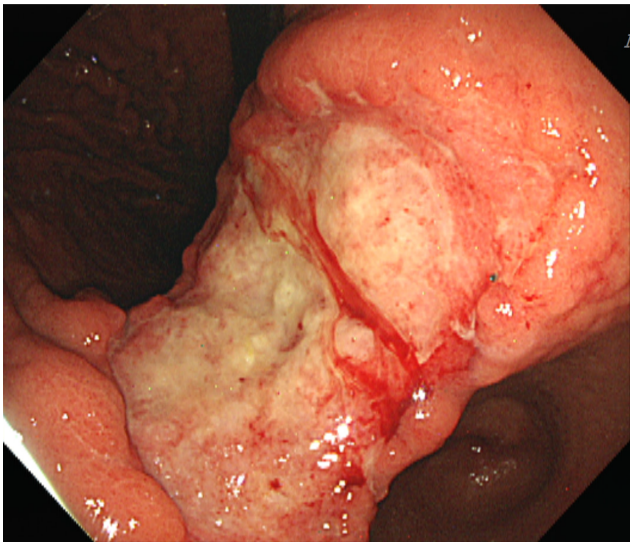

Figure 2 Endoscopic finding. A huge irregular ulcerative lesion in the gastric cardia.

Barr virus all showed negative results.

Imaging examinations

To investigate the cause of the patient's primary symptom, an esophagogastroduodenoscopy was first performed, revealing a large irregular ulcerative lesion in the gastric cardia (Figure 2). This endoscopic finding was clinically suspected as advanced gastric cancer. Thus, a biopsy was performed.

After confirmation of the biopsy result, to determine the stage of the lymphoma, the patient underwent imaging tests, including abdominal and pelvic computed tomography (CT) scans and 18F-fluorodeoxyglucose-positron emission tomography/CT scans (Figure 3). These imaging studies showed the involvement of stomach and intra-abdominal lymph nodes.

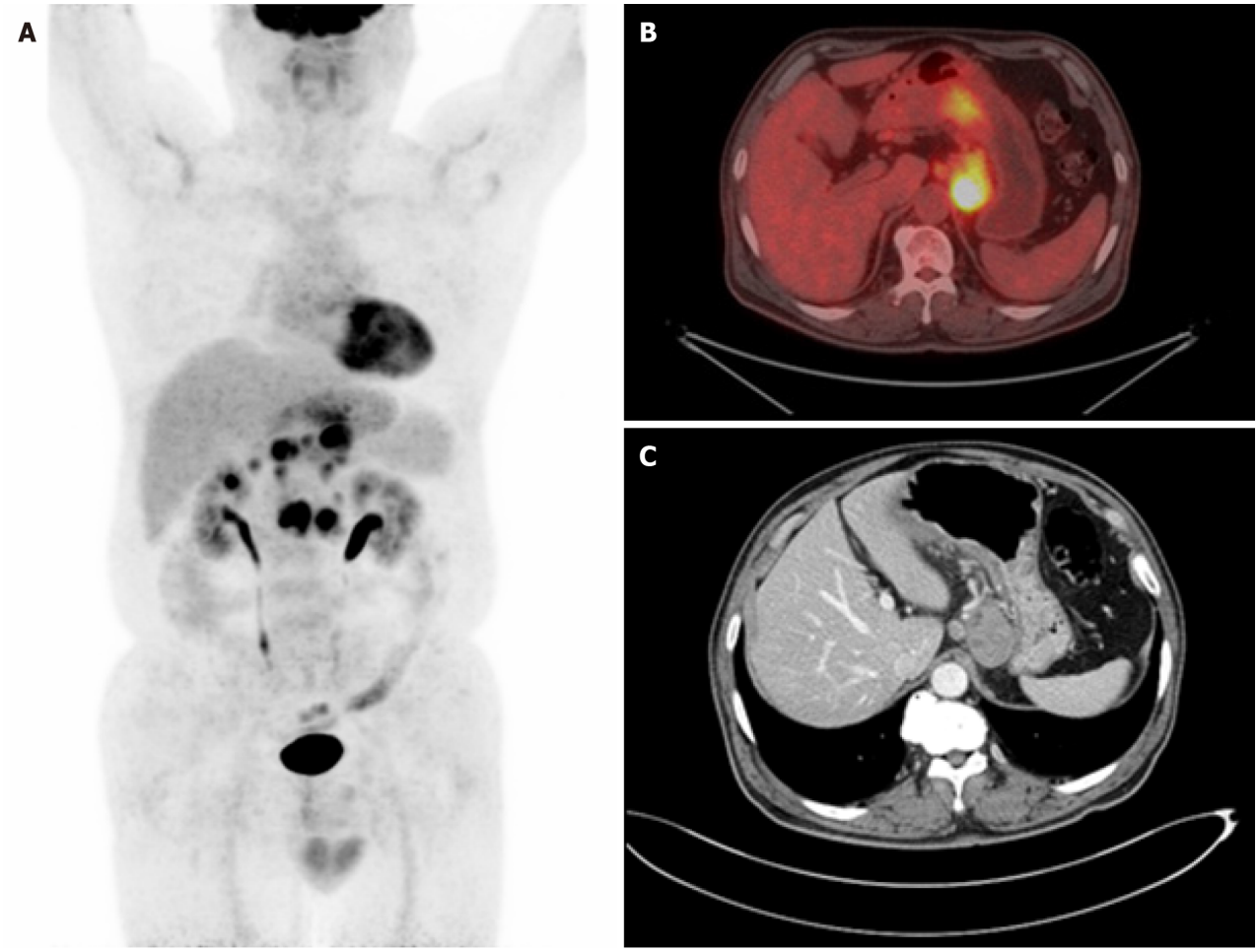

Figure 3 Underwent imaging. A and B: Positron emission tomography showed hypermetabolic mass located in the lower body; C: Computed tomography showed diffuse wall thickening of the posterior lesser curvature of the gastric body with metastatic nodes.

FINAL DIAGNOSIS

Based on these findings, the patient received a diagnosis of PTCL-NOS, meeting the diagnostic criteria for intestinal T-cell lymphoma, not otherwise specified based on the revised World Health Organization 2018 classification.

TREATMENT

The patient underwent a bone marrow examination, which confirmed that there was no lymphoma involvement in the bone marrow. The final staging was determined to be stage II. The patient received a total of six cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide.

OUTCOME AND FOLLOW-UP

The patient did not experience any significant complications or treatment-related adverse events throughout the chemotherapy. Complete remission was confirmed after six cycles of chemotherapy.

DISCUSSION

Primary gastric PTCL-NOS is a rare subtype of lymphoma. As a result, report about its prevalence is limited. Among several subtypes of T-cell lymphoma, EATL appears to be the most common subtype of gastric T-cell lymphoma according to several studies. It has been reported that EATL accounts for 12%-40% of all gastric T-cell lymphomas[6,7].

In a study on primary GI lymphoma conducted in China, 415 patients with primary GI lymphoma were identified between 1998 and 2013. Among these cases, T-cell lymphoma was reported in approximately 60 cases. Specifically, PG-

Table 1 Treatment approaches and outcomes for primary gastric T-cell lymphoma: Summary of literatures

Ref.	Study period (year)	Study type	Sample size	Patients with gastric peripheral T-cell lymphoma-not otherwise specified	Patient demographics	Treatment	Outcomes
Park *et al*[9]	1990-2004	Primary gastric lymphoma of T-cell origin	17	7 (41.1)	Median age 49 years, male (14 : 3)	CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide, Vanderbilt regimen, surgical resection	Median progression-free survival 10 months, median OS 12 months
Kim *et al*[8]	1995-2008	Endoscopic and clinical analysis of primary T-cell lymphoma of the GI tract	36	5 (13.9)	Median age 50 years, male to female ratio 2.6:1	Of the 36 patients, primary surgical resection with chemotherapy (55%), primary chemotherapy without surgery (45%)	Median OS 7.8 months, 3-year survival rate 19.4%
Kohri *et al* [10]	2007-2018	Peripheral T-cell lymphoma with GI involvement	11	2 (2.4)	Median age 75 years, 10 males and 1 female	CHOP	OS 7 months and 83 months (2 patients)
Zhang *et al*[5]	1975-2016	Gastric T-cell lymphoma in the SEER program	164	104 (63.4)	Median age 65 years, mostly White and male	Chemotherapy, surgery, radiotherapy	Median OS 8 months, 5-year OS 23.5%

CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; GI: Gastrointestinal; OS: overall survival.

TCL was reported in about 7 cases[6]. The study from China provided limited information regarding specific subtypes of T-cell lymphoma. According to SEER data analysis, from 1965 to 2016, a total of 164 patients with PG-TCL were analyzed. The age-adjusted occurrence rate of PG-TCL stood at 0.0091 per 100000 person-years and demonstrated an increase in frequency as age advanced. This incidence rate is about 1/20000 of the incidence rate of B-cell lymphoma. The present report also showed that its occurrence varied depending on ethnicity and geographic location. Patients with primary gastric PTCL-NOS showed distinctive clinical characteristics such as younger age at disease onset, higher incidence among males, less prevalence among white race, advanced disease stage, and frequent presence of symptom B. Furthermore, overall survival and cancer-specific survival rates of primary gastric PTCL-NOS patients were significantly lower than those of patients with other subtypes of gastric lymphoma[5]. Nevertheless, these two studies demonstrate that primary gastric PTCL-NOS is an exceedingly rare disease. It is important to note that endoscopic findings of primary gastric lymphoma can be nonspecific. They can resemble those of other gastric diseases such as gastric adenocarcinoma and peptic ulcer disease[8]. Therefore, histopathologic examination is required for a definitive diagnosis.

The optimal management for primary gastric PTCL-NOS has not been established yet. Although there was no specific research exclusively focusing on PTCL-NOS, retrospective studies related to the treatment of T-cell lineage gastric lymphoma indicated that the majority of patients received a combination therapy of cyclophosphamide, doxorubicin, vincristine, and prednisone[9,10]. Table 1 summarizes the studies that have investigated the treatment strategies and outcomes for patients with primary gastric PTCL-NOS. Treatment outcomes were evaluated based on disease status, with results ranging from death due to the disease to survival durations lasting from 7 months to over 83 months[5,8-10].

Primary gastric PTCL-NOS is rare, as it is typically found in other organs such as the small bowel rather than the stomach. B-cell lymphomas are more commonly associated with gastric involvement. However, in cases where gastric lymphoma is suspected, despite its low incidence, it is crucial to conduct appropriate testing for the diagnosis of T-cell lymphoma, known to have a poor prognosis. This approach can provide valuable insights and guide appropriate treatment decisions.

CONCLUSION

We present a case of gastric PTCL-NOS, a condition that is seldom discussed in relation to it endoscopic findings and the process of pathological differential diagnosis. This case is notable due to the rarity of gastric PTCL-NOS.

FOOTNOTES

Author contributions: Jang HR organized the data and drafted the manuscript; Lee K contributed to writing and reviewing the pathology findings; Lim KH designed the study and contributed to the manuscript writing; all of the authors read and approved the final version of the manuscript to be published.

Supported by 2024 Kangwon National University Hospital Grant, No. KNUH_2024_02_06.

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

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

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: South Korea

ORCID number: Hee Ryeong Jang 0000-0001-8162-8657; Kyungyul Lee 0000-0002-6243-6868; Kyu-Hyoung Lim 0000-0001-8284-9198.

S-Editor: Luo ML
L-Editor: A
P-Editor: Wang WB

REFERENCES

1 **Bautista-Quach MA**, Ake CD, Chen M, Wang J. Gastrointestinal lymphomas: Morphology, immunophenotype and molecular features. *J Gastrointest Oncol* 2012; **3**: 209-225 [PMID: 22943012 DOI: 10.3978/j.issn.2078-6891.2012.024]
2 **Groves FD**, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst* 2000; **92**: 1240-1251 [PMID: 10922409 DOI: 10.1093/jnci/92.15.1240]
3 **Peng JC**, Zhong L, Ran ZH. Primary lymphomas in the gastrointestinal tract. *J Dig Dis* 2015; **16**: 169-176 [PMID: 25678011 DOI: 10.1111/1751-2980.12234]
4 **Morton JE**, Leyland MJ, Vaughan Hudson G, Vaughan Hudson B, Anderson L, Bennett MH, MacLennan KA. Primary gastrointestinal non-Hodgkin's lymphoma: a review of 175 British National Lymphoma Investigation cases. *Br J Cancer* 1993; **67**: 776-782 [PMID: 8471435 DOI: 10.1038/bjc.1993.141]
5 **Zhang M**, Xiao F, Lin M, Chen M, Hou J, Huang H. The epidemiology and prognosis of patients with primary gastric T-cell lymphoma in the SEER program. *Cancer Med* 2023; **12**: 84-98 [PMID: 35698430 DOI: 10.1002/cam4.4936]
6 **Chen Y**, Chen Y, Chen S, Wu L, Xu L, Lian G, Yang K, Li Y, Zeng L, Huang K. Primary Gastrointestinal Lymphoma: A Retrospective Multicenter Clinical Study of 415 Cases in Chinese Province of Guangdong and a Systematic Review Containing 5075 Chinese Patients. *Medicine (Baltimore)* 2015; **94**: e2119 [PMID: 26632732 DOI: 10.1097/MD.0000000000002119]
7 **Tse E**, Gill H, Loong F, Kim SJ, Ng SB, Tang T, Ko YH, Chng WJ, Lim ST, Kim WS, Kwong YL. Type II enteropathy-associated T-cell lymphoma: a multicenter analysis from the Asia Lymphoma Study Group. *Am J Hematol* 2012; **87**: 663-668 [PMID: 22641357 DOI: 10.1002/ajh.23213]
8 **Kim DH**, Lee D, Kim JW, Huh J, Park SH, Ha HK, Suh C, Yoon SM, Kim KJ, Choi KD, Ye BD, Byeon JS, Song HJ, Jung HY, Yang SK, Kim JH, Myung SJ. Endoscopic and clinical analysis of primary T-cell lymphoma of the gastrointestinal tract according to pathological subtype. *J Gastroenterol Hepatol* 2014; **29**: 934-943 [PMID: 24325295 DOI: 10.1111/jgh.12471]
9 **Park YH**, Kim WS, Bang SM, Lee SI, Kang HJ, Na II, Yang SH, Lee SS, Uhm JE, Kwon JM, Kim K, Jung CW, Park K, Ko YH, Ryoo BY. Primary gastric lymphoma of T-cell origin: clinicopathologic features and treatment outcome. *Leuk Res* 2006; **30**: 1253-1258 [PMID: 16529813 DOI: 10.1016/j.leukres.2006.01.018]
10 **Kohri M**, Tsukasaki K, Akuzawa Y, Tanae K, Takahashi N, Saeki T, Okamura D, Ishikawa M, Maeda T, Kawai N, Matsuda A, Arai E, Arai S, Asou N. Peripheral T-cell lymphoma with gastrointestinal involvement and indolent T-lymphoproliferative disorders of the gastrointestinal tract. *Leuk Res* 2020; **91**: 106336 [PMID: 32151888 DOI: 10.1016/j.leukres.2020.106336]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6840-6847

DOI: 10.12998/wjcc.v12.i35.6840

ISSN 2307-8960 (online)

CASE REPORT

Cat scratch disease in children with nocturnal fever: A case report

Qi-Ling Yin, You-Qiong Liu, Hui-Min Zhang, Ya-Le Zhang, Shu-Min Qi, Jin-Quan Wen, Wei-Hua Zhang

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

P-Reviewer: Hasibuzzaman MA

Received: August 10, 2024
Revised: September 11, 2024
Accepted: October 10, 2024
Published online: December 16, 2024
Processing time: 74 Days and 17.3 Hours

Qi-Ling Yin, You-Qiong Liu, Hui-Min Zhang, Department of Pediatric, Shaanxi University of Chinese Medicine, Xianyang 721000, Shaanxi Province, China

Ya-Le Zhang, Department of Pediatric Respiratory, Rainbow Hospital of Xianyang (Children's Hospital of Xianyang), Xianyang 721000, Shaanxi Province, China

Shu-Min Qi, Department of Pathology, Rainbow Hospital of Xianyang (Children's Hospital of Xianyang), Xianyang 721000, Shaanxi Province, China

Jin-Quan Wen, Department of Pediatric Hematology/Oncology, Rainbow Hospital of Xianyang (Children's Hospital of Xianyang), Xianyang 721000, Shaanxi Province, China

Wei-Hua Zhang, Department of Pediatric Intensive Care Unit, Rainbow Hospital of Xianyang (Children's Hospital of Xianyang), Xianyang 721000, Shaanxi Province, China

Co-first authors: Qi-Ling Yin and You-Qiong Liu.

Corresponding author: Wei-Hua Zhang, Doctor, Associate Chief Physician, Department of Pediatric Intensive Care Unit, Rainbow Hospital of Xianyang (Children's Hospital of Xianyang), No. 3 Weiyang West Road, Qindu District, Xianyang 721000, Shaanxi Province, China. xiangyuelanda2006@126.com

Abstract

BACKGROUND

Cat scratch disease (CSD) is the most common human infection caused by *Bartonella henselae* (*B. henselae*). The main manifestation is self-limited lymphadenopathy that primarily affects adolescents, and typically resolves without treatment within 2-4 months. However, individuals with compromised immune systems or immunodeficiency require specific antibacterial therapy following diagnosis. Due to its low incidence, nonspecific clinical manifestations, and diagnostic limitations, this condition often poses challenges for clinicians in terms of missed diagnoses and misdiagnoses.

CASE SUMMARY

The child was ultimately diagnosed with CSD. The primary manifestations included nocturnal fever, enlargement of lymph nodes in the neck, axilla and groin, and suspected brucellosis; however, both brucellosis tests conducted during the course of the illness yielded negative results. Bone marrow cytology indicated stimulated proliferation. Lymph node biopsy indicated hyperplasia of lymphoid tissue in the cervical lymph nodes (right), with combined immunohistochemical findings indicating reactive hyperplasia. Immunohistochemical analysis

revealed CD20 B (+), CD3 T (+), BCL-6 (+), and BCL-2 (-). CD21 FDC networks were present and Ki67 expression in the germinal center was ~80%. Blood next-generation sequencing indicated *B. henselae* sequence number was 3. Serological test results demonstrated positive antibody response to *B. henselae* IgG (+), *B. henselae* IgM (+), *Bartonella quintana* (*B. quintana*) IgG (-) and *B. quintana* IgM (-), and the final diagnosis was CSD.

CONCLUSION
In patients presenting with fever at night and swollen lymph nodes of unknown origin, CSD should be considered.

Key Words: *Bartonella henselae*; Cat scratch disease; Nocturnal fever; Children; Case report

Core Tip: We report a case of cat scratch disease (CSD) characterized by nocturnal fever as the primary manifestation, accompanied by cervical and inguinal lymphadenopathy. In patients presenting with fever of unknown origin as the predominant symptom, a comprehensive physical examination and thorough medical history are essential to minimize the risk of missed or incorrect diagnosis. CSD is typically self-limiting and often does not require treatment, and symptomatic management and regular follow-up suffice for patients with milder symptoms. However, special attention should be given to immunodeficient and immunocompromised individuals who may require timely antimicrobial therapy.

Citation: Yin QL, Liu YQ, Zhang HM, Zhang YL, Qi SM, Wen JQ, Zhang WH. Cat scratch disease in children with nocturnal fever: A case report. *World J Clin Cases* 2024; 12(35): 6840-6847
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6840.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6840

INTRODUCTION

Cat scratch disease (CSD) is a zoonotic infectious disease. The main host is mammals, and it is transmitted by hematophagous insects such as phlebotomine sandflies, human body lice and cat fleas, or introduced into humans through biting and clawing by cats[1,2]. Most typical CSD is characterized by self-limited regional lymph node enlargement or lymphadenitis, usually associated with systemic symptoms, and 10% of patients show involvement of other organs, indicating atypical CSD[3,4]. We here report a child diagnosed with CSD whose main presentation was nocturnal fever, and discuss its clinical significance.

CASE PRESENTATION

Chief complaints

A 4-year-old girl of Han nationality was admitted to the Pediatric Respiratory Department of Xianyang Rainbow Hospital, China on December 30, 2023. The girl had intermittent fever for 14 d, cough for 6 d, with the neck, axillary and inguinal lymph node enlargement.

History of present illness

Her fever occurred 14 days ago without an apparent cause, reaching a peak temperature of 40.0 ℃. The parents administered oral medication for 2 days, but there was no improvement. Subsequently, she was treated with azithromycin and cefuroxime at a local clinic for 8 days; however, the therapeutic effect was unsatisfactory. During the course of treatment, coughing persisted and necessitated comprehensive care at a local hospital for 5 days. Upon review, it was observed that the relevant inflammation index continued to rise and she still experienced recurrent fever with a peak temperature of 40.0 ℃.

History of past illness

There was no history of past illness.

Personal and family history

There was no personal and family history.

Physical examination

Temperature: 36.8 ℃, pulse: 94 beats/minute, respiratory rate: 24 breaths/minute, blood pressure: 92/54 mmHg, body weight 17 kg. Alertness and cooperation were good. No rash or bleeding spots were observed throughout the body.

Soybean-sized enlarged lymph nodes were palpable in the neck, axilla and groin, which were soft, nontender and had good mobility. The remaining superficial lymph nodes were not palpable. The conjunctivas were not hyperemic. The lips were not cyanotic, bayberry tongue was positive, the oral mucosa was smooth, pharyngeal hyperemia was obvious, the tonsils were enlarged II°, and no purulent secretions were observed. The neck was soft and without resistance. On auscultation, heart and lung sounds were normal, abdominal examination was normal and nervous system examination was normal.

Laboratory examinations

Initial blood tests showed the following (December 29, 2023): Hemoglobin 114 g/L; white blood cell (WBC) count: 10.19 × 10^9/L; platelet count: 213 × 10^9/L; serum amyloid A (SAA): 156.3 mg/L; C-reactive protein (CRP) 156.3 mg/L; erythrocyte sedimentation rate (ESR): 40 mm/hour; interleukin (IL)-6: 24.05 pg/mL; *Mycobacterium tuberculosis* antibody (-); ferritin: 92.19 ng/mL; Epstein-Barr virus (EBV)-IgG (-) and EBV-IgM (-); brucellosis agglutination test: < 1: 25 (-).

Imaging examinations

Chest computed tomography (CT) revealed bronchiolitis in both lungs and small nodular lesions in the upper lobe of the left lung.

FINAL DIAGNOSIS

The patient was finally diagnosed with CSD.

TREATMENT

On days 1 and 2, the patient was given symptomatic and supportive treatment. Blood tests showed: Hemoglobin: 99 g/L; WBC count: 4.50 × 10^9/L; platelet count: 274 × 10^9/L; ESR: 52 mm/hour; high-sensitivity (hs)-CRP: 56.70 mg/L; CRP: 50.90 mg/L; and SAA: 251.6 mg/L. Subsets of lymphocytes, thyroid function, immunoglobulin, IL-6, antistreptolysin, rheumatoid factor, electrolytes, procalcitonin, myocardial enzymes, tumor markers, tuberculous IgG antibody and epidemic hemorrhagic fever virus antibody were all negative. Ultrasound showed bilaterally enlarged cervical lymph nodes, splenomegaly, right renal cyst, but no obvious heart and coronary artery anomalies.

On days 3 and 4, she continued to experience recurrent fever, reaching a peak temperature of 39.4 °C, accompanied by paroxysmal coughing. Nucleic acid detection for six respiratory viruses showed parainfluenza I RNA (+). IL-6 10.72 level was pg/mL and IFN-γ 96.02 pg/mL. *Mycoplasma pneumoniae* DNA, EBV DNA, *Bordetella pertussis* DNA, enterovirus, *Chlamydia pneumoniae* antibody, and novel coronavirus nucleic acid were all negative. CT revealed no discernible abnormalities in the brain, paranasal sinus or abdomen.

On days 5 and 7, she still had fever, and the highest temperature was 39.8 °C. The fever was reduced to normal levels through administration of oral antipyretics and alleviation of paroxysmal coughing. Blood next-generation sequencing (NGS) revealed that sequence number of *Bartonella henselae* (*B. henselae*) was 3. Autoantibody, anti-neutrophil cytoplasmic antibody, T-Spot and sputum culture were negative. Further enquiry about the patient's medical history revealed that she kept dogs and cats at home. Her mother complained that the patient was scratched by a cat 3-4 months ago. CSD was suspected and trimethoprim/sulfamethoxazole (TMP/SMX) was administered.

On days 8 and 9, she presented with nocturnal fever, while remaining afebrile during the day. Furthermore, the duration between fever episodes increased compared to previous occurrences.

On days 10 to 12, she still had nocturnal fever. Blood cell morphology smear showed that red blood cells were a consistent size, with a pale area of light staining. WBCs were predominantly granulocytes, with some toxic granules. Platelets were scattered in the visible. In order to exclude hematological disorders and necrotizing lymphadenitis, with the consent of the families, bone marrow puncture and biopsy analysis were performed.

On days 13 to 16 the nocturnal fever persisted, with *B. henselae* IgG (+) and IgM (+). Reports of bone marrow cytology and lymph node biopsy pathology are presented in the next section. She was diagnosed with CSD, and the treatment regimen was adjusted from TMP/SMZ to doxycycline.

On days 17 to 20, her temperature remained within the normal range, and the specific serological test for *Brucella* was negative. Subsequent re-examination of blood, CRP, hs-CRP, ESR and SAA was normal. Therefore, she was discharged and doxycycline was maintained for 1 wk. Her temperature records are shown in Figure 1.

OUTCOME AND FOLLOW-UP

Bone marrow cytology showed proliferation (Figure 2). Lymph node biopsy showed hyperplasia of lymphoid tissue in the cervical lymph nodes (right; Figure 3). Lymph node biopsy immunohistochemical analysis showed CD20 B (+), CD3 T (+), BCL-6 (+) and BCL-2 (-). CD21 FDC networks were present (+) and Ki67 expression in the germinal center was approximately 80%. All the findings indicated reactive hyperplasia (Figure 4).

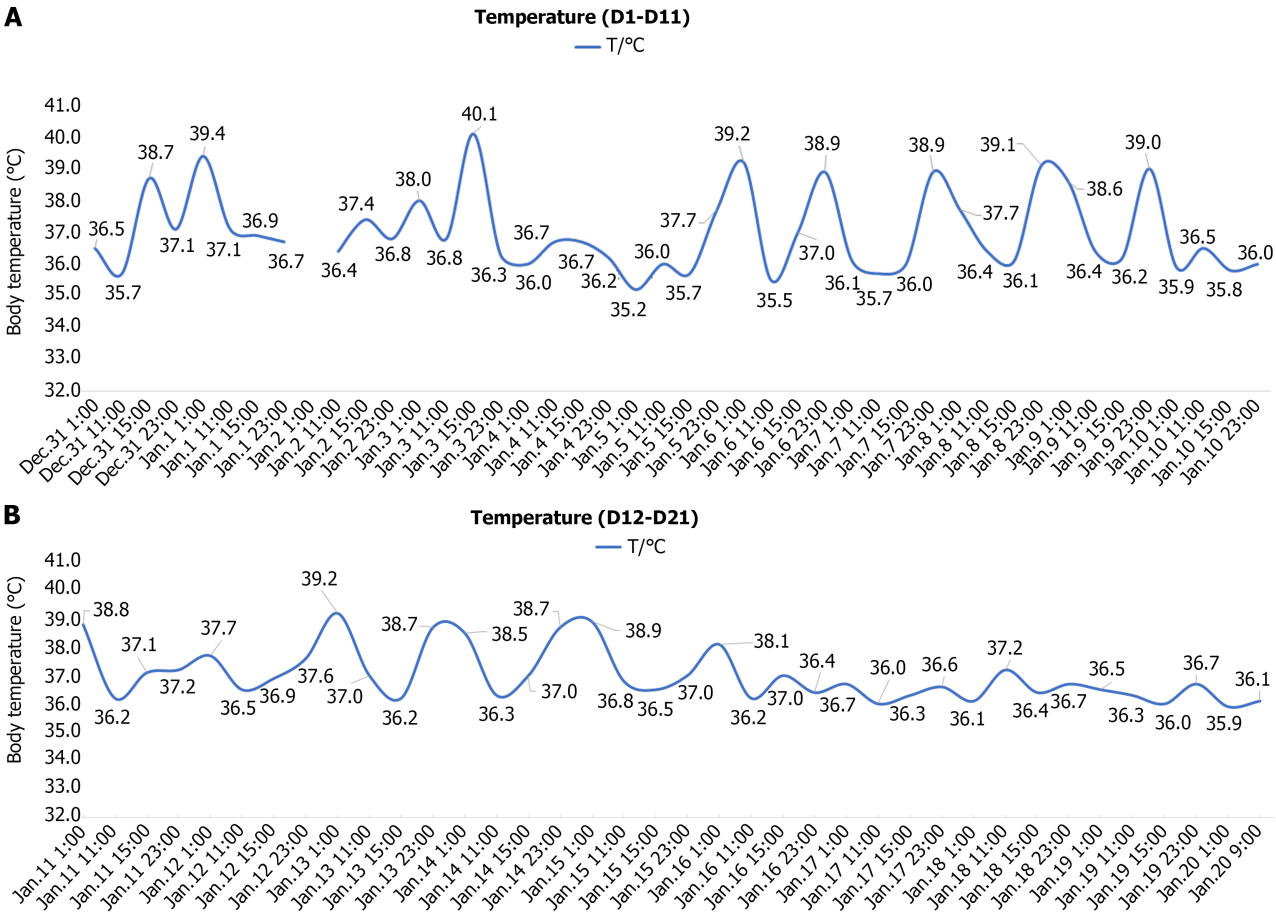

Figure 1 Temperature records. A: Days 1–11; B: Days 12–21.

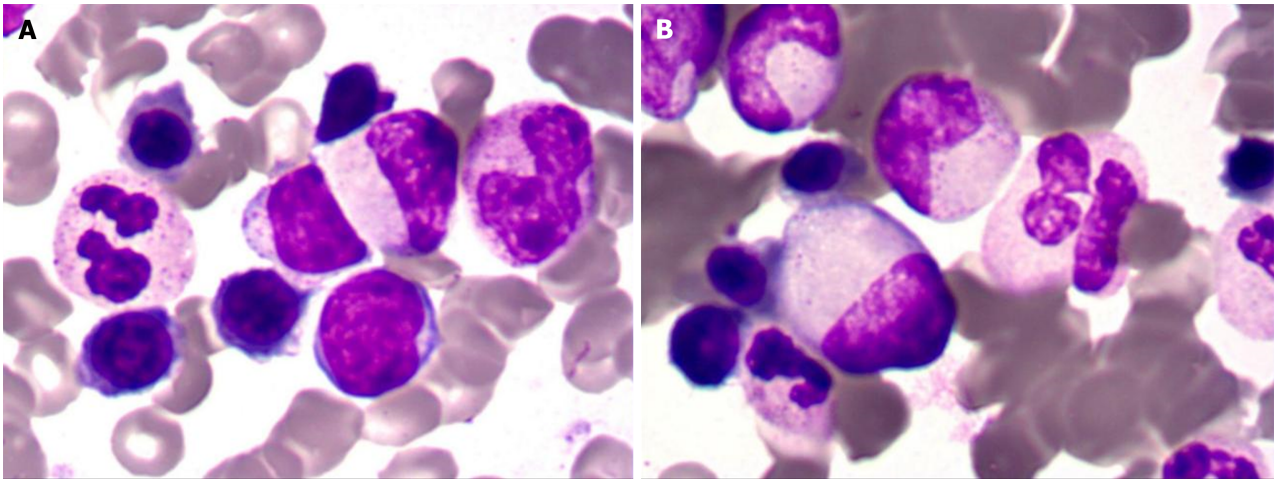

Figure 2 Bone marrow cytology. A: Bone marrow cytology; B: Bone marrow cytology.

After doxycycline treatment, the body temperature returned to normal and all clinical symptoms resolved. She was discharged on day 20. Follow-up examination of routine blood tests, CRP, ESR, and hepatic and renal function revealed no significant abnormalities 1 and 2 months later. Her temperature returned to the normal range.

DISCUSSION

Fever of unknown origin (FUO) refers to a body temperature of ≥ 38.3 ℃ on at least two occasions, persisting for a duration of ≥ 3 three weeks, or having multiple febrile episodes over this time period. There must be no obvious diagnosis despite comprehensive medical history collection and examination, as well as appropriate tests including

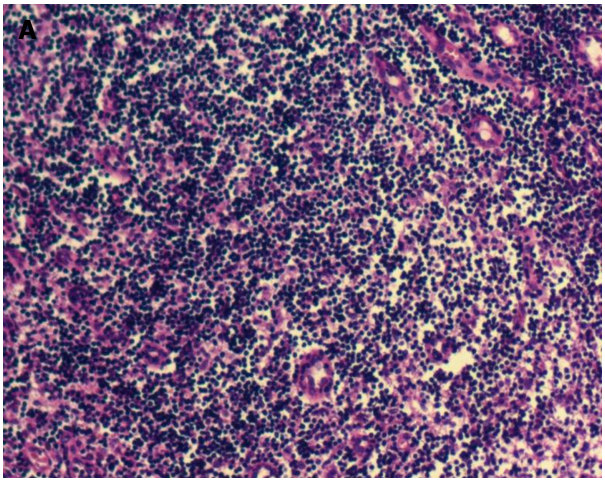

Figure 3 Lymph node biopsy pathology.

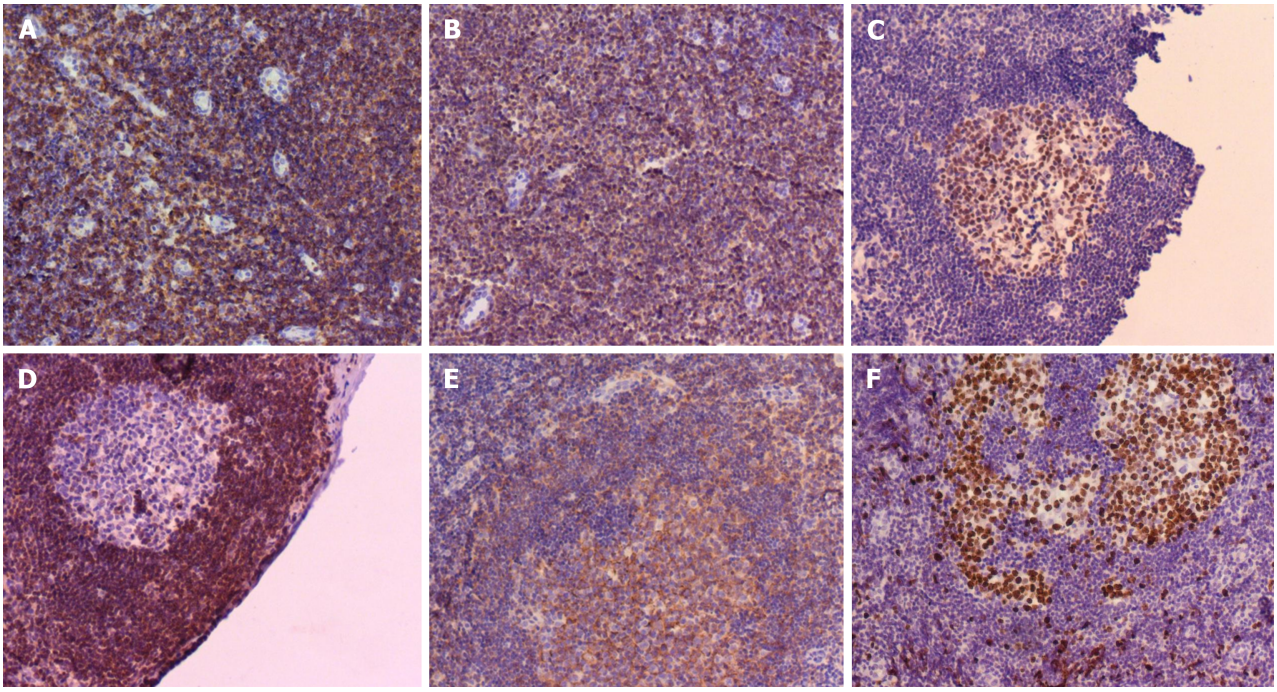

Figure 4 Lymph node biopsy immunohistochemical analysis. A: CD20 B (+); B: CD3 T (+); C: BCL-6 (+); D: BCL-2 (-); E: CD21 FDC (+); F: Ki67 (+).

routine blood tests, inflammatory markers, autoimmune screening, cultures, chest radiography and abdominal imaging [5]. There are > 200 potential causes of FUO which can be broadly categorized into infectious diseases, neoplastic diseases, noninfectious inflammatory diseases, and other conditions. The patient presented with FUO lasting for 28 d prior to establishment of a definitive diagnosis[6].

The primary manifestation of this case was nocturnal fever, accompanied by enlargement of cervical, axillary and inguinal lymph nodes. The fever type did not meet the characteristics of continuous, remittent, intermittent, recurrent or undulant fever commonly observed in brucellosis[7]. Brucellosis typically presents with symptoms such as fever, fatigue, night sweats and joint pain. The characteristic pattern is nocturnal fever and sweating that subsides in the morning. Clinical symptoms and physical examination are usually nonspecific; however, lymphadenopathy along with hepatomegaly or splenomegaly may be present. Brucellosis is a zoonotic disease caused by Gram-negative bacteria from the genus *Brucella*. It is mainly transmitted through consumption of raw milk and milk products or contact with infected animals or their feces. Its clinical symptoms often overlap with other febrile diseases[8]. Our patient was admitted to the hospital with FUO as the chief complaint, accompanied by neck, axillary and inguinal lymph node enlargement. The possibility of brucellosis was considered high because of the history of cats and dogs at home, the course of the disease with persistent fever for several weeks, sweating, enlarged lymph nodes, and fever characterized by nocturnal fever. Abdominal ultrasound revealed splenomegaly which suggested brucellosis; however, the agglutination tests for brucellosis were negative twice, and therefore were not considered for the time being. After further history taking it was discovered that a cat had scratched the patient 3-4 months ago. Combined with the child's clinical symptoms, CSD was

considered, so relevant serological tests and metagenomic NGS (mNGS) were done. Blood NGS revealed that sequence number of *B. henselae* was 3, and positive IgM/IgG for *B. henselae*, which led to the final diagnosis of CSD[9-11].

CSD is a self-limiting disease caused by *B. henselae*. It is the most common cause of regional lymphadenitis in children and adolescents during late summer and autumn. The pathogenesis of CSD is still unclear. Some researchers believe that *Bartonella* induces a proinflammatory response by upregulating expression of cell adhesion molecules on endothelial cells, leading to local infection[12]. In the United States, the incidence of CSD is highest in children aged 5–9 years, with 12500 patients diagnosed with CSD each year; 500 of whom require hospitalization[13]. The clinical spectrum of CSD ranges from asymptomatic infection to multiorgan involvement. Approximately 90% of patients present with typical CSD, characterized by self-limiting regional lymphadenopathy or lymphadenitis. Around 30% of patients experience systemic symptoms, including fever, chills, night sweats, headache and abdominal pain. Atypical CSD occurs in approximately 10% of cases and is associated with tissue and organ involvement beyond the lymph nodes such as the eyes, nervous system, heart, liver, spleen, skin or musculoskeletal system (*e.g.*, erythema nodosum and neuroretinitis). These manifestations are more commonly observed in immunocompromised individuals who have a higher risk for complications[14].

The diagnostic criteria for CSD include the following: (1) Exposure to cats or fleas, with or without scratches or local inoculation lesions (such as skin papules, eye granulomas, and mucous membranes); (2) Laboratory/radiology findings: negative purified protein derivative or serology for other infectious causes of adenopathy; sterile pus aspirated from lymph nodes, polymerase chain reaction assay positive; *B. henselae*, *B. quintana* or *Afipia felis*: Highest sensitivity. CT scan: liver/spleen abscesses; (3) Positive ELISA or indirect fluorescent antibody test and serological titer > 1:64 for *B. henselae* are indicative. A fourfold increase in titer between acute and convalescent samples is also suggestive; and (4) Biopsy of lymph nodes, skin, liver, bone, or eye granuloma showing granulomatous inflammation compatible with CSD; positive Warthin–Starry silver stain. If three of the four criteria are met, a diagnosis of CSD can be made. In atypical cases, four criteria must be met[15]. CSD should be considered when a patient presents with persistent or chronic lymph node enlargement (≥ 10 mm) for > 3 weeks. However, due to the prolonged incubation period of CSD, patients often fail to provide an epidemiological history during their doctor visits. There is no gold-standard method for the diagnosis of CSD and the commonly used rates of misdiagnosis and underdiagnosis are usually high. Current examination techniques for diagnosis of CSD include serological testing, PCR, and tissue biopsy. Of these, serological tests are the most commonly used, such as immunofluorescent antibody test and enzyme immunoassay, which are considered highly suggestive of a recent infection when the IgG value is > 1:256; the production of IgM is usually transient. *Bartonella* culture yields rare positive results and requires stringent conditions, while antigen and antibody detection are not routinely performed in most hospitals. However, serological sensitivity is also limited and there is significant cross reactivity with other microorganisms. PCR is a specific method for detecting *Bartonella* infections, and although PCR detection at the lesion site is both specific and sensitive, it necessitates invasive collection of tissue or pus samples from the affected area, which may lead to infection spread and low patient acceptance, and its diagnostic value is limited in patients with low levels of bacteremia. Tissue biopsy is an invasive examination and not the first choice for doctors, and cytology and pathology findings do not have specificity in diagnosing CSD. Although mNGS offers higher sensitivity compared to traditional culture methods and enables rapid identification of pathogens, its analysis and interpretation can be complicated by sample contamination, reagent processing issues, or microbial contaminants present within the laboratory environment. mNGS is expensive and not typically chosen as a first-line option by clinicians for CSD diagnosis. Therefore, laboratory diagnosis of CSD remains challenging[16-20]. For the early identification and diagnosis of CSD, clinicians must, firstly, ask patients in detail whether they have a history of cat exposure; secondly, choose the appropriate investigations in combination with the patient's medical history and clinical symptoms; and lastly, regardless of the time of year, CSD needs to be taken into account in the case of lymph node enlargement with unexplained fever.

The need for antimicrobial treatment of CSD depends on the clinical manifestations and immune function of the patient. For patients with normal immune function or mild disease, antibiotic treatment is generally not necessary and self-healing occurs within 2–4 months. Timely and standardized antimicrobial therapy should be used for patients with low immunity, immunodeficiency or severe illness[21]. *B. henselae* is a small, curved, aerobic Gram-negative bacillus that stains with silver. In bacillary angiomatosis, lobular proliferation of small blood vessels occurs with the presence of bacilli in adjacent connective tissue and blood vessels. New combinations of antibiotics with bactericidal effects and enhanced cellular lipid barrier penetration should be considered for the treatment of bartonellosis. Macrolides and tetracyclines are recommended as first-line therapy due to their superior intracellular activity. The results of an *in vitro* susceptibility study in 2006 demonstrated that *Bartonella* is susceptible to many antibiotics. However, considering *Bartonella*'s characteristics as an intracellular bacterium, it is advisable to utilize intracellular bactericides such as macrolides, tetracyclines and rifampicin for anti-infective treatment[15,22]. The Infectious Diseases Society of America[23] recommends azithromycin for CSD treatment. When azithromycin cannot be used, TMP/SMZ serves as a reasonable alternative. Doxycycline has shown efficacy in severe neuroretinitis, endocarditis or chronic bacteremia caused by *Bartonella*[24]. In the management of patients with CSD, we need timely and regular follow-up visits to closely observe the changes in the patient's condition, especially for patients with immunodeficiency.

CONCLUSION

Our patient presented with nocturnal fever and lymphadenopathy as the primary clinical manifestations. The administration of azithromycin and TMP/SMZ were not effective and the patient recovered after receiving oral doxycycline. This highlights the importance for clinicians to remain vigilant for CSD when encountering patients with nocturnal fever.

ACKNOWLEDGEMENTS

We thank the Metagenomics Next-generation Sequencing Technology Research Center of Anlong Gene for its technological support.

FOOTNOTES

Author contributions: Yin QL and Liu YQ contributed equally to this study as co-first authors. Both of two authors have made equally significant contributions to the work and share equal responsibility and accountability for it. Yin QL and Zhang WH contributed to conception and design of the study; Zhang HM and Qi SM collected histopathological data; Zhang YL and Liu YQ organized the database; Yin QL drafted the manuscript; all authors contributed to manuscript revision, and have read and approved the submitted version.

Supported by Shaanxi Natural Science Foundation, No. 2020SF-004.

Informed consent statement: The study participant's legal guardian, provided informed written consent prior to study enrollment.

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

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: China

ORCID number: Qi-Ling Yin 0009-0007-7318-9747; You-Qiong Liu 0009-0004-5333-5143; Hui-Min Zhang 0009-0001-8659-6700; Ya-Le Zhang 0009-0007-2936-7104; Shu-Min Qi 0009-0000-8088-8115; Jin-Quan Wen 0000-0001-9202-6598; Wei-Hua Zhang 0000-0002-4579-3492.

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

REFERENCES

1 **Chomel BB**. Cat-scratch disease. *Rev Sci Tech* 2000; **19**: 136-150 [PMID: 11189710 DOI: 10.20506/rst.19.1.1204]
2 **Pecora F**, Abate L, Scavone S, Petrucci I, Costa F, Caminiti C, Argentiero A, Esposito S. Management of Infectious Lymphadenitis in Children. *Children (Basel)* 2021; **8** [PMID: 34682125 DOI: 10.3390/children8100860]
3 **Nawrocki CC**, Max RJ, Marzec NS, Nelson CA. Atypical Manifestations of Cat-Scratch Disease, United States, 2005-2014. *Emerg Infect Dis* 2020; **26**: 1438-1446 [PMID: 32568056 DOI: 10.3201/eid2607.200034]
4 **Deregibus MI**, Bagnara EI, Buchovsky A. Cat-scratch disease: Experience in a tertiary care children's hospital. *Arch Argent Pediatr* 2023; **121**: e202202592 [PMID: 36315437 DOI: 10.5546/aap.2022-02592.eng]
5 **Hu B**, Chen TM, Liu SP, Hu HL, Guo LY, Chen HY, Li SY, Liu G. Fever of unknown origin (FUO) in children: a single-centre experience from Beijing, China. *BMJ Open* 2022; **12**: e049840 [PMID: 35296470 DOI: 10.1136/bmjopen-2021-049840]
6 **Santana LFE**, Rodrigues MS, Silva MPA, Brito RJVC, Nicacio JM, Duarte RMSC, Gomes OV. Fever of unknown origin - a literature review. *Rev Assoc Med Bras (1992)* 2019; **65**: 1109-1115 [PMID: 31531611 DOI: 10.1590/1806-9282.65.8.1109]
7 **Qureshi KA**, Parvez A, Fahmy NA, Abdel Hady BH, Kumar S, Ganguly A, Atiya A, Elhassan GO, Alfadly SO, Parkkila S, Aspatwar A. Brucellosis: epidemiology, pathogenesis, diagnosis and treatment-a comprehensive review. *Ann Med* 2023; **55**: 2295398 [PMID: 38165919 DOI: 10.1080/07853890.2023.2295398]
8 **Wu ZG**, Song ZY, Wang WX, Xi WN, Jin D, Ai MX, Wu YC, Lan Y, Song SF, Zhang GC, Yao XB, Gao Z, Liu CY, Sun K, Yu DS, Xie BG, Sun SL. Human brucellosis and fever of unknown origin. *BMC Infect Dis* 2022; **22**: 868 [PMID: 36411430 DOI: 10.1186/s12879-022-07872-8]
9 **Zhou T**, Zheng Y, Zhang H, Liu Y. A case report of diagnosis of cat-scratch disease using metagenomic next-generation sequencing. *Front Cell Infect Microbiol* 2023; **13**: 1322651 [PMID: 38287977 DOI: 10.3389/fcimb.2023.1322651]
10 **Li P**, Qian Z, Tao Y. Application of metagenomic next-generation sequencing in the diagnosis of Bartonella neuroretinitis: a case report and literature review. *J Ophthalmic Inflamm Infect* 2024; **14**: 17 [PMID: 38637335 DOI: 10.1186/s12348-024-00387-0]
11 **Allizond V**, Costa C, Sidoti F, Scutera S, Bianco G, Sparti R, Banche G, Dalmasso P, Cuffini AM, Cavallo R, Musso T. Serological and molecular detection of Bartonella henselae in specimens from patients with suspected cat scratch disease in Italy: A comparative study. *PLoS One* 2019; **14**: e0211945 [PMID: 30735549 DOI: 10.1371/journal.pone.0211945]
12 **Chomel BB**, Kasten RW. Bartonellosis, an increasingly recognized zoonosis. *J Appl Microbiol* 2010; **109**: 743-750 [PMID: 20148999 DOI: 10.1111/j.1365-2672.2010.04679.x]
13 **Nelson CA**, Saha S, Mead PS. Cat-Scratch Disease in the United States, 2005-2013. *Emerg Infect Dis* 2016; **22**: 1741-1746 [PMID: 27648778

DOI: 10.3201/eid2210.160115]

14 **Maiques-Tobias E**, Tomatis-Souverbielle C, Watson J, Ramilo O, Mejias A. [Disseminated cat scratch disease: The wide variety of clinical presentations]. *An Pediatr (Engl Ed)* 2019; **90**: 393-395 [PMID: 31167731 DOI: 10.1016/j.anpedi.2018.06.002]

15 **Margileth AM**. Recent Advances in Diagnosis and Treatment of Cat Scratch Disease. *Curr Infect Dis Rep* 2000; **2**: 141-146 [PMID: 11095849 DOI: 10.1007/s11908-000-0026-8]

16 **Hempel A**, Manzoor F, Petrescu D. Hemophagocytic lymphohistiocytosis secondary to unrecognized Bartonella henselae infection: a case report. *Trop Dis Travel Med Vaccines* 2023; **9**: 14 [PMID: 37743475 DOI: 10.1186/s40794-023-00200-1]

17 **Koutantou M**, Kambas K, Makka S, Fournier PE, Raoult D, Angelakis E. Limitations of Serological Diagnosis of Typical Cat Scratch Disease and Recommendations for the Diagnostic Procedure. *Can J Infect Dis Med Microbiol* 2023; **2023**: 4222511 [PMID: 36915870 DOI: 10.1155/2023/4222511]

18 **Sander A**, Berner R, Ruess M. Serodiagnosis of cat scratch disease: response to Bartonella henselae in children and a review of diagnostic methods. *Eur J Clin Microbiol Infect Dis* 2001; **20**: 392-401 [PMID: 11476439 DOI: 10.1007/pl00011280]

19 **Vaca DJ**, Dobler G, Fischer SF, Keller C, Konrad M, von Loewenich FD, Orenga S, Sapre SU, van Belkum A, Kempf VAJ. Contemporary diagnostics for medically relevant fastidious microorganisms belonging to the genera Anaplasma,Bartonella,Coxiella,OrientiaandRickettsia. *FEMS Microbiol Rev* 2022; **46** [PMID: 35175353 DOI: 10.1093/femsre/fuac013]

20 **Li M**, Yan K, Jia P, Wei E, Wang H. Metagenomic next-generation sequencing may assist diagnosis of cat-scratch disease. *Front Cell Infect Microbiol* 2022; **12**: 946849 [PMID: 36189365 DOI: 10.3389/fcimb.2022.946849]

21 **Biancardi AL**, Curi AL. Cat-scratch disease. *Ocul Immunol Inflamm* 2014; **22**: 148-154 [PMID: 24107122 DOI: 10.3109/09273948.2013.833631]

22 **Conrad DA**. Treatment of cat-scratch disease. *Curr Opin Pediatr* 2001; **13**: 56-59 [PMID: 11176245 DOI: 10.1097/00008480-200102000-00010]

23 **Shorbatli LA**, Koranyi KI, Nahata MC. Effectiveness of antibiotic therapy in pediatric patients with cat scratch disease. *Int J Clin Pharm* 2018; **40**: 1458-1461 [PMID: 30446895 DOI: 10.1007/s11096-018-0746-1]

24 **Avaylon J**, Lau K, Harter K, Mamoor A, Mehendale R, Ranasinghe L, Durant E, Bains G. Neuroretinitis as a Complication of Cat Scratch Disease. *Cureus* 2023; **15**: e45866 [PMID: 37885521 DOI: 10.7759/cureus.45866]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6848-6850

DOI: 10.12998/wjcc.v12.i35.6848

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Understanding network meta-analysis

Sunny Chi Lik Au

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: Javaid ZK

Received: March 13, 2024
Revised: September 22, 2024
Accepted: October 8, 2024
Published online: December 16, 2024
Processing time: 224 Days and 19.1 Hours

Sunny Chi Lik Au, Department of Ophthalmology, Tung Wah Eastern Hospital, Hong Kong 999077, China

Corresponding author: Sunny Chi Lik Au, MBChB, Chief Doctor, Surgeon, Department of Ophthalmology, Tung Wah Eastern Hospital, Lo Ka Chow Memorial Ophthalmic Centre, No. 19 Eastern Hospital Road, Causeway Bay, Hong Kong 999077, China. kilihcua@gmail.com

Abstract

Recently, in the *World Journal of Clinical Cases*, studied the different non-steroidal anti-inflammatory drugs (meloxicam, celecoxib, naproxen, and rofecoxib) for juvenile idiopathic arthritis with network meta-analysis (NMA). This manuscript aims to introduce to clinicians what NMA is. NMA represents a fundamental technique for simultaneously comparing three or more interventions within a single analysis, harnessing both direct and indirect evidence derived from a network of studies. It surpasses pair-wise meta-analysis which are confined to direct comparison of two items in clinical trials. This approach can estimate the relative effects between any pair of interventions within the network, often yielding more precise estimations than those generated from single direct or indirect analyses. NMA necessitates steps akin to those of conventional meta-analysis, involving a thorough literature search, assessment of potential trial biases, statistical analysis of reported pairwise comparisons for all relevant outcomes, and evaluation of overall certainty of evidence on an outcome-specific basis. However, NMA demands substantial resources, given its propensity to address broader inquiries, typically involving a larger number of studies at each phase of the systematic review, from screening to analysis, compared to traditional meta-analyses.

Key Words: Meta-analysis; Systematic review; Methodology; Research; Journal; Academic

Core Tip: Network meta-analysis stands as a potent instrument for comparative research of three or more. It surpasses pair-wise meta-analysis in complexity. Additionally, supplementary analyses, such as network meta-regression further elevate the intricacy of the analysis.

Citation: Au SCL. Understanding network meta-analysis. *World J Clin Cases* 2024; 12(35): 6848-6850
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6848.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6848

TO THE EDITOR

Meta-analysis is a statistical tool for pooling data and results across different studies hoping to arrive on a more precise conclusions to a clinical question. However, traditional meta-analyses are notably confined to direct comparison of two items (either intervention or treatment) in clinical trials. In reality, numerous trials contain more than one single active therapeutic arm comparing against placebos, usual practice, or the current standard of care as primary outcomes; whereas the comparison of results across different interventions may be the secondary outcomes. In response to these limitations, network meta-analysis (NMA) has emerged, enabling the computation of comparative effects among more than two interventions, even when lacking direct comparison within clinical trials.

NMA represents a fundamental technique for simultaneously comparing three or more interventions within a single analysis, harnessing both direct and indirect evidence derived from a network of studies. Zeng *et al*[1] studied the different non-steroidal anti-inflammatory drugs (meloxicam, celecoxib, naproxen, and rofecoxib) for juvenile idiopathic arthritis with NMA. This approach can estimate the relative effects between any pair of interventions within the network, often yielding more precise estimations than those generated from single direct or indirect analyses. Moreover, it facilitates the estimation of rankings and hierarchies of interventions[2].

HOW DOES NMA BEGIN

NMA necessitates steps akin to those of conventional meta-analysis, involving a thorough literature search, assessment of potential trial biases, statistical analysis of reported pairwise comparisons for all relevant outcomes, and evaluation of overall certainty of evidence on an outcome-specific basis. Zeng *et al*[1] thoroughly searched over different databases, and yielded 755 results. They also listed out the bias assessment of each study. NMA then identifies interventions linked by a common comparator. For instance, distinct active treatments may have been compared against placebos in separate trials. NMA enables the creation of a hypothetical trial comparing these active treatments based on their effects against a shared placebo, generating "indirect" evidence. These indirect comparisons serve to bridge knowledge gaps within existing evidence, yielding a more comprehensive understanding of treatment alternatives for clinicians. Once all treatments within a network have been compared, various methods exist for ranking treatments, conveying their relative net effectiveness[3].

The validity of NMA lies on the assumption that studies included in the analysis are similar in all major factors that would not induce a significant relative effect across studies. However, incoherence, also known as inconsistency, emerges when different input studies' results were contradicting to each other's. Grading confidence of evidence derived from a NMA commences with a meticulous evaluation of confidence in each direct comparison[4]. Domain-specific assessments were subsequently combined to evaluate the overall confidence in the evidence, encapsulating the multifaceted nature of this analytical approach while underscoring its potential impact on clinical decision-making and policy formation.

The utilization of a NMA encompasses the advantages of all accessible direct and indirect evidence. Research studies have indicated that this approach yields estimations of intervention effects with greater precision compared to individual direct or indirect estimates[5]. Moreover, it offers the capacity to furnish comparative data for interventions that have not been individually assessed within randomized trials[6]. This concurrent comparison of all pertinent interventions within a single analysis facilitates the estimation of their relative ranking concerning a specified outcome.

CONCLUSIONS

NMA stands as a potent instrument for comparative research of three or more. It surpasses pair-wise meta-analysis in complexity. Additionally, supplementary analyses, such as network meta-regression further elevate the intricacy of the analysis[7]. Notably, NMA demands substantial resources, given its propensity to address broader inquiries, typically involving a larger number of studies at each phase of the systematic review, from screening to analysis, compared to traditional meta-analyses.

FOOTNOTES

Author contributions: Au SCL designed the research, acquired the data, performed the analysis and interpretation of data, and drafted and revised the article; the author read and approved the final version of the manuscript to be published.

Conflict-of-interest statement: The author declares no conflict of interest in publishing the manuscript.

Country of origin: China

ORCID number: Sunny Chi Lik Au 0000-0002-5849-3317.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Zeng T**, Ye JZ, Qin H, Xu QQ. Systematic review and network meta-analysis of different non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis. *World J Clin Cases* 2024; **12**: 2056-2064 [PMID: 38680254 DOI: 10.12998/wjcc.v12.i12.2056]
2 **Rouse B**, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med* 2017; **12**: 103-111 [PMID: 27913917 DOI: 10.1007/s11739-016-1583-7]
3 **Phillips MR**, Steel DH, Wykoff CC, Busse JW, Bannuru RR, Thabane L, Bhandari M, Chaudhary V; Retina Evidence Trials InterNational Alliance (R. E.T.I.N.A.) Study Group. A clinician's guide to network meta-analysis. *Eye (Lond)* 2022; **36**: 1523-1526 [PMID: 35145277 DOI: 10.1038/s41433-022-01943-5]
4 **Dias S**, Caldwell DM. Network meta-analysis explained. *Arch Dis Child Fetal Neonatal Ed* 2019; **104**: F8-F12 [PMID: 30425115 DOI: 10.1136/archdischild-2018-315224]
5 **Cooper NJ**, Peters J, Lai MC, Juni P, Wandel S, Palmer S, Paulden M, Conti S, Welton NJ, Abrams KR, Bujkiewicz S, Spiegelhalter D, Sutton AJ. How valuable are multiple treatment comparison methods in evidence-based health-care evaluation? *Value Health* 2011; **14**: 371-380 [PMID: 21296599 DOI: 10.1016/j.jval.2010.09.001]
6 **Caldwell DM**, Dias S, Welton NJ. Extending Treatment Networks in Health Technology Assessment: How Far Should We Go? *Value Health* 2015; **18**: 673-681 [PMID: 26297096 DOI: 10.1016/j.jval.2015.03.1792]
7 **Puerto Nino AK**, Brignardello-Petersen R. How To Read a Network Meta-analysis. *Eur Urol Focus* 2023; **9**: 701-704 [PMID: 37925328 DOI: 10.1016/j.euf.2023.10.018]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6851-6854

DOI: 10.12998/wjcc.v12.i35.6851

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Effects of foot reflexology on disease

Ming-Ying He, M Jalal Ud Din, Hai-Feng Xu, Shang-Yu Wang, Guo-Huan Ying, Hao Qian, Bing Wu, Hong-Dan Qi, Xin Wang, Gang 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 A

Creativity or Innovation: Grade A

Scientific Significance: Grade B

P-Reviewer: Alsuliman RM

Received: March 18, 2024

Revised: September 19, 2024

Accepted: October 9, 2024

Published online: December 16, 2024

Processing time: 220 Days and 4.5 Hours

Ming-Ying He, Hai-Feng Xu, Shang-Yu Wang, Guo-Huan Ying, Hao Qian, Bing Wu, Hong-Dan Qi, Xin Wang, Gang Zhang, Department of Neurology, Children's Hospital of Nanjing Medical University, Nanjing 210008, Jiangsu Province, China

M Jalal Ud Din, Department of Neurology, Nanjing Medical University, Nanjing 210000, Jiangsu Province, China

Corresponding author: Gang Zhang, Doctor, PhD, Associate Professor, Chief Doctor, Postdoc, Department of Neurology, Children's Hospital of Nanjing Medical University, No. 72 Guangzhou Road, Nanjing 210008, Jiangsu Province, China. zhanggangnjmu@126.com

Abstract

In this article, we review a recently published article to explore the significance of foot reflexology in modern medical practice. With the advancement of modern medicine, we are increasingly committed to finding the specific physiological mechanisms of foot reflexes to treat diseases, thereby better proving the therapy's effectiveness. It has been reported that foot reflexes can activate the cerebral cortex and organs corresponding to the feet, stimulating blood flow, nutrition and nerves through neural and endocrine regulation to achieve the purpose of treating and preventing diseases and promoting health. The therapy shows unique potential and value, and provides a new perspective on integrating traditional medicine and modern medicine.

Key Words: Foot; Reflexology; Sense-hearing loss; Alternative medicine; Massage therapy

Core Tip: Most of the previous studies on foot reflexology have been systematic reviews, with mixed results. There has been one case report that foot reflexology can treat sensory-hearing loss, which provides objective imaging evidence to increase its credibility. However, the number of included studies is too small, and a large sample randomized controlled trial is needed to further study the mechanism of foot reflexology to prove its effectiveness.

Citation: He MY, Ud Din MJ, Xu HF, Wang SY, Ying GH, Qian H, Wu B, Qi HD, Wang X, Zhang G. Effects of foot reflexology on disease. *World J Clin Cases* 2024; 12(35): 6851-6854
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6851.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6851

TO THE EDITOR

Foot reflexology, also known as zone therapy or reflexology massage, is based on the principle that specific areas on the soles of the feet correspond to other parts of the body and organs. By applying appropriate pressure and stimulation to these areas, it is believed that these reflex zones can be activated, promoting therapeutic effects by stimulating blood flow, nutrients, nerves, *etc*. According to research, foot reflexology can help alleviate pain, exhaustion, cancer symptoms, sleep disturbances, and other health problems[1]. This low-cost, side-effects-free, simple and non-invasive complementary therapy is becoming popular in the general population.

DISCUSSION

A review of clinical randomized controlled trials (RCTs) on foot reflexology therapy for various conditions concluded that foot reflexology therapy is effective in treating premenstrual syndrome[2]. A systematic review and meta-analysis of 44 relevant studies on the effects of foot reflexology on fatigue, sleep, and pain was conducted in 2011. Of these, 15 studies investigated fatigue, 18 sleep, and 11 pain. The study concluded that while foot reflexology can help with fatigue and sleep promotion, it is less successful with pain[3]. Foot reflexology was shown to be effective in treating fecal incontinence and chronic constipation in 50 children aged 3 to 14 years who participated in an observational study. The majority of the children improved without experiencing any side effects, and 72% of the parents expressed high satisfaction with the children's treatment[4]. In 2010, a study found that foot massage effectively reduced postoperative pain intensity in Turkish pregnant women, in contrast to a control observation group, indicating its potential in pain management[5]. In a clinical study comparing the effects of foot and palm reflexology on respiratory distress in infants with noninvasive ventilation, statistically significant differences in mean oxygen saturation percentage, respiratory rate and respiratory distress score were found between the two intervention and control groups ($P < 0.05$). Both types of reflexology effectively alleviated respiratory distress in preterm infants receiving noninvasive ventilation[6]. In a systematic review of the impact of foot reflexology on patients with multiple sclerosis (MS), which included nine studies with a total of 545 patients, it was found that foot reflexology can help reduce physical symptoms such as fatigue, pain, muscle spasms and stiffness, as well as alleviate psychological symptoms and improve quality of life in patients with MS. However, larger, high-quality studies are needed to further validate the efficacy of this therapy[7]. In 2009, a systematic review was conducted on reflexology for a variety of conditions including anovulation, asthma, back pain, dementia, diabetes, gestational foot edema, irritable bowel syndrome, and MS. Although reflexology was found to have positive therapeutic benefits, most RCTs were of poor quality, did not adequately control for non-specific effects, and most had small sample sizes. Two large RCTs (n = 130 and 243) yielded negative results, with most having one RCT and lacking independent replication, indicating insufficient evidence on the effectiveness of reflexology in treating diseases[8]. Does foot reflexology have any therapeutic effects? We found that previous studies were mainly clinical case reports and systematic reviews, which lacked relevant mechanistic studies and other objective evidence to support the effectiveness of this treatment. This makes it difficult to convince people of the benefits of foot reflexology. Encouragingly, recent literature conclusively shows that foot reflexology stimulation activates somatosensory responses to the stimulated reflexology area. Three reflexology areas in the left foot associated with the eye, shoulder, and small intestine were identified. Reflexology stimulation of these areas not only activates the somatosensory region corresponding to the foot, but also the somatosensory region corresponding to neighboring body parts. This process was verified using functional magnetic resonance imaging (fMRI), which captures signals from active brain areas due to increased neuronal activity and blood flow, allowing a better understanding of surrounding tissues[9]. The report supports the Chinese conjecture that specific areas of the soles of the feet correspond to other parts and organs of the body. Foot massage therapy also accelerates the maturation of electroencephalography activity and visual function (including vision) in human infants and rat pups, mediated by upregulation of insulin-like growth factor-1-positive neurons. This study confirmed the efficacy of foot reflexology in treating diseases, thereby enhancing our confidence in this therapy[10]. Foot reflexology can improve vagus nerve function, reduce sympathetic nerve regulation, lower blood pressure, decrease depression and stress responses, and enhance the immune system in middle-aged women[11]. A recent case report, "Effect of foot reflexology on an infant with sensorineural hearing loss: A case report", which found that foot reflexology can treat sensorineural deafness, which is caused by damage or dysfunction of the cochlear or auditory nerves. This type of hearing loss usually cannot be restored with medical or surgical treatment, but hearing can be improved with assistive devices such as hearing aids or cochlear implants. We recorded the changes of functional connectivity in the brain of children with sensorineural hearing loss after receiving foot reflexology massage. The regional synchronicity of the upper frontal lobe, the lower frontal lobe and the right middle temporal lobe of the treated children increased. These brain regions are mainly involved in language processing and speech perception, which indicates that foot reflexology can promote the improvement of these functions, thus improving hearing and language development in children. The objective physiological basis of fMRI

is supported in this paper, and the language level of children at the later stage of follow-up was comparable to that of normal children of the same age. The scientific basis for the clinical application of foot reflexology in treating sensorineural deafness has been demonstrated[12]. The successful treatment of sensorineural hearing loss in infants with foot reflexology is promising, but the small sample size in the study is insufficient to prove its universal applicability. A larger sample size is needed to verify the reliability of the treatment results. Combining fMRI with other imaging techniques such as diffuse tensor imaging and positron emission tomography can provide a better understanding of changes in brain functional connectivity and structure. Studies should consider individual differences, age groups, and disease severity which could provide better results. Foot reflexology can improve prognosis, reduce the costs associated with hearing aids, and enhance patient welfare.

Foot massage can be traced back to the ancient Egyptian civilization. In traditional Chinese culture, foot massage is often closely linked with health and health care. In Southeast Asian countries, foot reflexology and the application of local herbs has become a characteristic cultural practice. In Europe and the United States is also favored by many people treated by professional reflexology therapists. Across different social cultures, foot reflexology is widespread and accepted by the public worldwide. To further enhance the scientific credibility and efficacy of foot reflexology, future research should focus on the following aspects: (1) Conduct large sample randomized controlled experiments to ensure the stability and repeatability of the results; (2) Examine the mechanism of action of foot reflexology therapy, including, but not limited to, nerve conduction, blood circulation improvement, endocrine regulation, immune response, *etc*., and observe the physiological changes during treatment with modern biological techniques and imaging methods to provide objective evidence on the therapeutic effect; Conduct basic experimental studies such as animal models to further validate and clarify the biological basis; (3) Conduct research on patients from different populations, different disease types and disease courses to determine the potential of foot reflexology in the treatment and prevention of diseases; (4) Long-term follow-up of patients treated with foot reflexology therapy should be performed to observe the continuity and stability of its efficacy; (5) Strengthen multidisciplinary cooperation and exchanges in medicine, biology, psychology, sociology, *etc*., and jointly promote the in-depth development of foot reflexology research; and (6) Develop standardized procedures and efficacy evaluation criteria for foot reflexology therapy to ensure comparability between studies.

CONCLUSION

Foot reflexology is a potentially effective healthcare intervention therapy. Foot massage can promote blood circulation throughout the body, relieve stress and anxiety, relieve chronic pain, regulate the endocrine system, *etc*. It shows great potential as a safe, effective and side-effect-free healthcare complementary therapy to promote overall health. However, current research on the effectiveness of foot reflexology has some limitations, including primarily focusing on systematic reviews and Meta-analyses with limited sample sizes, a lack of mechanistic studies, and insufficient supporting evidence. Further in-depth research is needed to uncover the scientific principles behind foot reflexology, to clarify its efficacy and credibility. As foot reflexology finds its unique place in modern healthcare practice as part of alternative medicine, it may hold promise for patients seeking low-cost, non-invasive treatment options. How much can foot reflexology contribute to chronic pain management, stress relief, and overall health? We encourage readers to explore these issues in depth. Perhaps it is through our efforts to determine the effects of foot reflexology that it may become an integral part of modern healthcare in the future.

ACKNOWLEDGEMENTS

Thanks to the relevant authors of the main study, who focused on foot reflexology to treat the disease, and gave me the opportunity to comment on this issue.

FOOTNOTES

Author contributions: He MY, Xu HF, Wang SY, Ying GH, Qian H, co-authored the analysis and wrote the article; Ud Din MJ, Wu B, Qi HD and Wang H made language changes. All authors approved the final manuscript for submission.

Conflict-of-interest statement: All the authors have no financial relationship with any commercial entity with a potential interest in the subject of this manuscript.

Country of origin: China

ORCID number: M Jalal Ud Din 0009-0004-9715-7940; Hai-Feng Xu 0009-0008-2053-0400; Shang-Yu Wang 0009-0004-9789-0325; Guo-Huan Ying 0009-0004-5914-1542; Hao Qian 0009-0006-1055-4527; Bing Wu 0009-0006-2065-3553; Hong-Dan Qi 0009-0001-7306-7818; Xin Wang

0009-0008-7343-1158; Gang Zhang 0000-0001-5729-7667.

S-Editor: Qu XL
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Wang MY**, Tsai PS, Lee PH, Chang WY, Yang CM. The efficacy of reflexology: systematic review. *J Adv Nurs* 2008; **62**: 512-520 [PMID: 18489444 DOI: 10.1111/j.1365-2648.2008.04606.x]
2 **Oleson T**, Flocco W. Randomized controlled study of premenstrual symptoms treated with ear, hand, and foot reflexology. *Obstet Gynecol* 1993; **82**: 906-911 [PMID: 8233263]
3 **Lee J**, Han M, Chung Y, Kim J, Choi J. Effects of foot reflexology on fatigue, sleep and pain: a systematic review and meta-analysis. *J Korean Acad Nurs* 2011; **41**: 821-833 [PMID: 22310867 DOI: 10.4040/jkan.2011.41.6.821]
4 **Bishop E**, McKinnon E, Weir E, Brown DW. Reflexology in the management of encopresis and chronic constipation. *Paediatr Nurs* 2003; **15**: 20-21 [PMID: 12715585 DOI: 10.7748/paed2003.04.15.3.20.c843]
5 **Miralizadeh A**, Peyman A, Jamali Soltani N, Ashktorab T. Comparison of the Effect of Foot and Palm Reflexology Massage on Respiratory Distress Syndrome in Premature Infants under Noninvasive Ventilation. *Complement Med Res* 2022; **29**: 100-108 [PMID: 34818220 DOI: 10.1159/000517982]
6 **Deenadayalan B**, Venugopal V, Poornima R, Kannan VM, Akila A, Yogapriya C, Maheshkumar K. Effect of Foot Reflexology on Patients With Multiple Sclerosis: A Systematic Review of Current Evidence. *Int J MS Care* 2024; **26**: 43-48 [PMID: 38482512 DOI: 10.7224/1537-2073.2022-093]
7 **Degirmen N**, Ozerdogan N, Sayiner D, Kosgeroglu N, Ayranci U. Effectiveness of foot and hand massage in postcesarean pain control in a group of Turkish pregnant women. *Appl Nurs Res* 2010; **23**: 153-158 [PMID: 20643325 DOI: 10.1016/j.apnr.2008.08.001]
8 **Ernst E**. Is reflexology an effective intervention? A systematic review of randomised controlled trials. *Med J Aust* 2009; **191**: 263-266 [PMID: 19740047 DOI: 10.5694/j.1326-5377.2009.tb02780.x]
9 **Miura N**, Akitsuki Y, Sekiguchi A, Kawashima R. Activity in the primary somatosensory cortex induced by reflexological stimulation is unaffected by pseudo-information: a functional magnetic resonance imaging study. *BMC Complement Altern Med* 2013; **13**: 114 [PMID: 23711332 DOI: 10.1186/1472-6882-13-114]
10 **Guzzetta A**, Baldini S, Bancale A, Baroncelli L, Ciucci F, Ghirri P, Putignano E, Sale A, Viegi A, Berardi N, Boldrini A, Cioni G, Maffei L. Massage accelerates brain development and the maturation of visual function. *J Neurosci* 2009; **29**: 6042-6051 [PMID: 19420271 DOI: 10.1523/JNEUROSCI.5548-08.2009]
11 **Lu WA**, Chen GY, Kuo CD. Foot reflexology can increase vagal modulation, decrease sympathetic modulation, and lower blood pressure in healthy subjects and patients with coronary artery disease. *Altern Ther Health Med* 2011; **17**: 8-14 [PMID: 22314629]
12 **Lee YJ**, Chen MQ, Dong J. Effect of foot reflexology on an infant with sensorineural hearing loss: A case report. *World J Clin Cases* 2024; **12**: 1437-1441 [PMID: 38576800 DOI: 10.12998/wjcc.v12.i8.1437]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6855-6858

DOI: 10.12998/wjcc.v12.i35.6855

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Clinical landscape and treatment of acute non-variceal upper gastrointestinal bleeding: Insights from a high-volume center in Shaanxi, China

Luca Improta

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

P-Reviewer: Pisarev VM

Received: March 19, 2024
Revised: September 8, 2024
Accepted: October 10, 2024
Published online: December 16, 2024
Processing time: 218 Days and 19.5 Hours

Luca Improta, Department of General Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, Rome 00128, Italy

Corresponding author: Luca Improta, MD, Chief Doctor, Department of General Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, *via* Alvaro del Portillo 200, Rome 00128, Italy. luca.dr.improta@gmail.com

Abstract

In this editorial we comment on the article by Wang *et al*, recently published on *World Journal of Clinical Cases*. Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) represents a common and potentially serious gastroenterological emergency. Wang *et al* conducted a detailed study on the management of ANVUGIB in a high-volume center in the Shaanxi region, China. Analyzing data from over 530 patients provided a comprehensive overview of clinical, epidemiological, and treatment characteristics. Results highlighted a younger patient population compared to European studies, with a higher prevalence of gastric and duodenal ulcers as the leading cause of bleeding. Endoscopic treatment is currently the preferred therapeutic option, offering a variety of effective techniques. This study emphasizes the importance of implementing current guidelines in ANVUGIB management and highlights the crucial role of endoscopy in its management.

Key Words: Upper gastrointestinal bleeding; Gastroenterological emergencies; Endoscopic treatment; Epidemiological characteristics; Clinical characteristics

Core Tip: Wang *et al* investigated acute non-variceal upper gastrointestinal bleeding management in a high-volume center in Shaanxi, China, revealing a younger patient demographic and a higher prevalence of gastric and duodenal ulcers as leading causes of bleeding compared to European studies. Endoscopic interventions emerged as the preferred therapeutic approach, emphasizing the importance of adhering to current guidelines and highlighting the pivotal role of endoscopy in treatment strategies.

Citation: Improta L. Clinical landscape and treatment of acute non-variceal upper gastrointestinal bleeding: Insights from a high-volume center in Shaanxi, China. *World J Clin Cases* 2024; 12(35): 6855-6858
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6855.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6855

TO THE EDITOR

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) certainly represents the gastroenterological emergency most frequently encountered by physicians in the emergency department. Despite the enormous progress made in the prevention and treatment of this condition over the last 50 years, and despite a gradual reduction in its incidence, ANVUGIB remains a challenging condition, still related to a non-negligible mortality rate. The most common cause of ANVUGIB is bleeding from gastric mucosal lesion, gastric and duodenal ulcers, while malignant disease is more frequent in the elderly[1,2].

The approach to ANVUGIB is described in detail by various validated international guidelines. An accurate stratification of patients upon presentation is crucial. Hemodynamic stabilization of patients in shock or pre-shock state is paramount, as is red blood cell transfusion in severely anemic patients. Subsequently, endoscopy should be performed within 24 hours of onset to promptly address all active sources of bleeding and high-risk lesions. There are multiple options for endoscopic treatment, with a success rate exceeding 90%. Currently, the most studied and practiced treatments are mechanical (application of endoscopic clips at the bleeding site) and thermal (diathermy coagulation, contact coagulation, or argon plasma coagulation), while more costly but promising are local treatments with the application of hemostatic materials. In case of recurrent bleeding, endoscopy remains the most effective therapeutic option, while in cases of endoscopic hemostasis failure and inability to achieve effective hemostasis, embolization or surgery remain valid alternatives[3-7].

The treatment of ANVUGIB in elderly patients with comorbidities is particularly complex and burdened by worse outcomes. These patients often present frailty due to pre-existing cardiovascular or pulmonary condition, and bleeding is frequently induced by chronic anticoagulant, antiplatelet, or anti-inflammatory therapies, or sometimes by unrecognized oncological pathology, or a combination of these factors. In these patients, even promptly treated ANVUGIB can be a disruptive first event in an already precarious balance[8-10].

In this scenario, it is crucial for the physician to be aware of both the epidemiological landscape of the area and the therapeutic options available to address this challenging condition.

In this issue of the Journal, Wang *et al*[11] describe and critically analyze the experience gained between 2021 and 2023 in ANVUGIB treatment at a high-volume center in the Shaanxi region of central China[11]. The authors meticulously delve into the clinical, epidemiological, and treatment characteristics of over 530 patients presenting with a final diagnosis of ANVUGIB, providing a significant snapshot of the clinical landscape in which they operate.

From the reading of Wang *et al*[11] work, several interesting considerations emerge. Firstly, it is interesting to note that, compared to European and North American statistics, the average age of patients diagnosed with ANVUGIB is lower in Wang *et al*[11] study. In the main studies published since the 1990s in Europe, the average age of patients at presentation is typically between 65 and 70 years, compared to the 53 years reported in the aforementioned study[12-14]. Moreover, when comparing recent studies with older historical series, a progressive and steady increase in the average age of patients can be observed[15,16]. This observation can partly be explained by several factors: The increasing average age of the population, the introduction of drugs effectively preventing gastric and duodenal ulcers–such as H2 receptor agonists in 1982 and proton pump inhibitors in 1990 the implementation of screening and treatment protocols for *Helicobacter pylori* infections, and the higher prevalence of chronic treatments with anticoagulants and aspirin in the elderly population.

While these factors have certainly had a global impact, it is important to consider that significant geographical differences persist. In Europe, for example, the average age of the population is itself significantly higher than in China, with a secondary direct impact on the total number of patients receiving anticoagulant and antiplatelet treatments. However, this single observation is not sufficient to justify the significant geographical difference found. Various studies explored genetic polymorphisms related to an increased risk of ANVUGIB, identifying several mutations affecting key molecular pathways governing platelet aggregation, inflammation, and angiogenesis[17]. It cannot be ruled out that such mutations may cluster in specific geographic regions, driving distinct epidemiological differences. It would be interesting to further explore with additional studies what population differences are involved and whether genetic polymorphism, lifestyle habits, dietary factors, or different healthcare policies are implicated.

Regarding etiology, it is known that historically the most common cause of ANVUGIB has been gastric and duodenal ulcers, which accounted for more than 40% of bleedings until the 1970s[15,18]. The temporal trend, also influenced by the introduction of effective medical treatments, has led to a progressive reduction in the incidence of this pathology, which is currently diagnosed in 20%-30% of patients[14]. Increasingly, the causes of ANVUGIB appear to be gastric and duodenal erosions, hemorrhagic gastritis, and other stress-related mucosal abnormalities, grouped under the definition of "mucosal abnormalities"[19]. Wang *et al*[11] describe the different causes of upper GI bleeding and find a prevalent incidence of gastric, duodenal, or complex ulcers except in elderly patients, where oncological pathology is the most frequent diagnosis. Interestingly, a new cause of ANVUGIB appeared in the literature since the implementation of ESD/EMR techniques as a complication of these procedures, although its systematic description and incidence is unclear, and we eagerly await further studies[20]. However, technological progress has laid the foundation for the current affirmation

of endoscopy as the treatment of choice in all cases of ANVUGIB.

Since the early experiences of hemostasis using high-frequency coagulation described by Hiratsuka in the early 1970s, endoscopic treatment has shown the potential to become the treatment of choice for ANVUGIB. In the following years, new treatments such as laser coagulation or heating probes and clips mechanical hemostasis have been described and widely adopted worldwide[21-23]. These treatments have immediately demonstrated efficacy rates exceeding 90%, with the added benefit of ensuring faster recovery and significantly lower complication rates compared to surgery[24]. Currently, several endoscopic treatments have been validated and, supported by robust scientific evidence, have been incorporated into all current international guidelines, constituting the present cornerstone of treatment[3-7]. Literature data confirm efficacy in controlling bleeding approaching 90%, regardless of the chosen method, and we can hope that the possibilities of endoscopic treatment will continue to grow with technological progress and the validation of new tools. Recently, over-the-scope clips, initially designed for endoscopic treatment of fistulas and perforations, have proven effective in controlling recurrent bleeding in large ulcers, while promising results are emerging from the study of new topical hemostatic agents[25,26].

Although the need for surgical intervention has decreased from 30% in the 1970s to 4% in more recent studies, there remains a proportion of ANVUGIB cases that cannot be treated endoscopically and are associated with a poorer prognosis[27]. Early identification of these patients and prompt referral for embolization or surgery can make a difference.

As highlighted in the work of Wang *et al*[11], despite potential geographical differences in clinical and epidemiological aspects, the implementation of current management protocols for ANVUGIB in accordance with the latest guidelines and scientific evidence ensures excellent chances of success. In this context, with the development of new tools and technologies, endoscopy will play an increasingly central role in the management of patients with ANVUGIB.

FOOTNOTES

Author contributions: Improta L elaborated, wrote and revised the manuscript.

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

Country of origin: Italy

ORCID number: Luca Improta 0000-0002-8915-1168.

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

REFERENCES

1 **Hearnshaw SA**, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011; **60**: 1327-1335 [PMID: 21490373 DOI: 10.1136/gut.2010.228437]

2 **Kate V**, Sureshkumar S, Gurushankari B, Kalayarasan R. Acute Upper Non-variceal and Lower Gastrointestinal Bleeding. *J Gastrointest Surg* 2022; **26**: 932-949 [PMID: 35083723 DOI: 10.1007/s11605-022-05258-4]

3 **Gralnek IM**, Dumonceau JM, Kuipers EJ, Lanas A, Sanders DS, Kurien M, Rotondano G, Hucl T, Dinis-Ribeiro M, Marmo R, Racz I, Arezzo A, Hoffmann RT, Lesur G, de Franchis R, Aabakken L, Veitch A, Radaelli F, Salgueiro P, Cardoso R, Maia L, Zullo A, Cipolletta L, Hassan C. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; **47**: a1-46 [PMID: 26417980 DOI: 10.1055/s-0034-1393172]

4 **Fujishiro M**, Iguchi M, Kakushima N, Kato M, Sakata Y, Hoteya S, Kataoka M, Shimaoka S, Yahagi N, Fujimoto K. Guidelines for endoscopic management of non-variceal upper gastrointestinal bleeding. *Dig Endosc* 2016; **28**: 363-378 [PMID: 26900095 DOI: 10.1111/den.12639]

5 **Bai Y**, Li ZS. Guidelines for the diagnosis and treatment of acute non-variceal upper gastrointestinal bleeding (2015, Nanchang, China). *J Dig Dis* 2016; **17**: 79-87 [PMID: 26853440 DOI: 10.1111/1751-2980.12319]

6 **Barkun AN**, Almadi M, Kuipers EJ, Laine L, Sung J, Tse F, Leontiadis GI, Abraham NS, Calvet X, Chan FKL, Douketis J, Enns R, Gralnek IM, Jairath V, Jensen D, Lau J, Lip GYH, Loffroy R, Maluf-Filho F, Meltzer AC, Reddy N, Saltzman JR, Marshall JK, Bardou M. Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group. *Ann Intern Med* 2019; **171**: 805-822 [PMID: 31634917 DOI: 10.7326/M19-1795]

7 **Laine L**, Barkun AN, Saltzman JR, Martel M, Leontiadis GI. ACG Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding. *Am J Gastroenterol* 2021; **116**: 899-917 [PMID: 33929377 DOI: 10.14309/ajg.0000000000001245]

8 **Marmo R**, Koch M, Cipolletta L, Capurso L, Pera A, Bianco MA, Rocca R, Dezi A, Fasoli R, Brunati S, Lorenzini I, Germani U, Di Matteo G, Giorgio P, Imperiali G, Minoli G, Barberani F, Boschetto S, Martorano M, Gatto G, Amuso M, Pastorelli A, Torre ES, Triossi O, Buzzi A,

Cestari R, Della Casa D, Proietti M, Tanzilli A, Aragona G, Giangregorio F, Allegretta L, Tronci S, Michetti P, Romagnoli P, Nucci A, Rogai F, Piubello W, Tebaldi M, Bonfante F, Casadei A, Cortini C, Chiozzini G, Girardi L, Leoci C, Bagnalasta G, Segato S, Chianese G, Salvagnini M, Rotondano G. Predictive factors of mortality from nonvariceal upper gastrointestinal hemorrhage: a multicenter study. *Am J Gastroenterol* 2008; **103**: 1639-1647; quiz 1648 [PMID: 18564127 DOI: 10.1111/j.1572-0241.2008.01865.x]

9 **Leontiadis GI**, Molloy-Bland M, Moayyedi P, Howden CW. Effect of comorbidity on mortality in patients with peptic ulcer bleeding: systematic review and meta-analysis. *Am J Gastroenterol* 2013; **108**: 331-345; quiz 346 [PMID: 23381016 DOI: 10.1038/ajg.2012.451]

10 **Stolow E**, Moreau C, Sayana H, Patel S. Management of Non-Variceal Upper GI Bleeding in the Geriatric Population: An Update. *Curr Gastroenterol Rep* 2021; **23**: 5 [PMID: 33768344 DOI: 10.1007/s11894-021-00805-6]

11 **Wang XJ**, Shi YP, Wang L, Li YN, Xu LJ, Zhang Y, Han S. Clinical characteristics of acute non-varicose upper gastrointestinal bleeding and the effect of endoscopic hemostasis. *World J Clin Cases* 2024; **12**: 1597-1605 [PMID: 38576734 DOI: 10.12998/wjcc.v12.i9.1597]

12 **Mamdani M**, Juurlink DN, Kopp A, Naglie G, Austin PC, Laupacis A. Gastrointestinal bleeding after the introduction of COX 2 inhibitors: ecological study. *BMJ* 2004; **328**: 1415-1416 [PMID: 15138157 DOI: 10.1136/bmj.38068.716262.F7]

13 **van Leerdam ME**, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, Tytgat GN. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am J Gastroenterol* 2003; **98**: 1494-1499 [PMID: 12873568 DOI: 10.1111/j.1572-0241.2003.07517.x]

14 **Di Fiore F**, Lecleire S, Merle V, Hervé S, Duhamel C, Dupas JL, Vandewalle A, Bental A, Gouerou H, Le Page M, Amouretti M, Czernichow P, Lerebours E. Changes in characteristics and outcome of acute upper gastrointestinal haemorrhage: a comparison of epidemiology and practices between 1996 and 2000 in a multicentre French study. *Eur J Gastroenterol Hepatol* 2005; **17**: 641-647 [PMID: 15879726 DOI: 10.1097/00042737-200506000-00008]

15 **Gilbert DA**, Silverstein FE, Tedesco FJ, Buenger NK, Persing J. The national ASGE survey on upper gastrointestinal bleeding. III. Endoscopy in upper gastrointestinal bleeding. *Gastrointest Endosc* 1981; **27**: 94-102 [PMID: 6971777 DOI: 10.1016/s0016-5107(81)73157-2]

16 **Allan R**, Dykes P. A Study of the Factors Influencing Mortality Rates from Gastrointestinal Haemorrhage. *QJM: An Int J Med* 1976; **45**: 533-550 [DOI: 10.1093/oxfordjournals.qjmed.a067479]

17 **Forgerini M**, Lucchetta RC, Urbano G, de Nadai TR, de Carvalho Mastroianni P. Genetic polymorphisms associated with upper gastrointestinal bleeding: a systematic review. *Pharmacogenomics J* 2021; **21**: 20-36 [PMID: 32948830 DOI: 10.1038/s41397-020-00185-6]

18 **Morgan AG**, McAdam WA, Walmsley GL, Jessop A, Horrocks JC, de Dombal FT. Clinical findings, early endoscopy, and multivariate analysis in patients bleeding from the upper gastrointestinal tract. *Br Med J* 1977; **2**: 237-240 [PMID: 301766 DOI: 10.1136/bmj.2.6081.237]

19 **Boonpongmanee S**, Fleischer DE, Pezzullo JC, Collier K, Mayoral W, Al-Kawas F, Chutkan R, Lewis JH, Tio TL, Benjamin SB. The frequency of peptic ulcer as a cause of upper-GI bleeding is exaggerated. *Gastrointest Endosc* 2004; **59**: 788-794 [PMID: 15173790 DOI: 10.1016/s0016-5107(04)00181-6]

20 **Wang Q**, Wu X, Jiang Q, Guo T, Feng Y, Wu D, Zhang S, Yang A. [Risk factors for bleeding during gastric endoscopic submucosal dissection]. *Zhonghua Xiaohua Neijing Zazhi* 2021; 38 [DOI: 10.3760/cma.j.cn321463-20200817-00539]

21 **Protell RL**, Rubin CE, Auth DC, Silverstein FE, Terou F, Dennis M, Piercey JR. The heater probe: a new endoscopic method for stopping massive gastrointestinal bleeding. *Gastroenterology* 1978; **74**: 257-262 [PMID: 620899 DOI: 10.1016/0016-5085(78)90807-7]

22 **Frühmorgen P**, Bodem F, Reidenbach HD, Kaduk B, Demling L. Endoscopic laser coagulation of bleeding gastrointestinal lesions with report of the first therapeutic application in man. *Gastrointest Endosc* 1976; **23**: 73-75 [PMID: 1086812 DOI: 10.1016/s0016-5107(76)73594-6]

23 **Hayashi T**. The Study on Stanch Clips for the Treatment by Endoscopy. *Gastrointest Endosc* 1975; 17 [DOI: 10.11280/gee1973b.17.92]

24 **Akasaka Y**, Shimizu S, Iwasaku A, Yoshinaka M, Inatomi I, Tada M, Kawai K. Clinical evaluation of heat probe method as endoscopic hemostasis for upper gi bleeding. *Gastrointest Endosc* 1986; 28 [DOI: 10.11280/gee1973b.28.1537]

25 **Hussein M**, Alzoubaidi D, Lopez MF, Weaver M, Ortiz-Fernandez-Sordo J, Bassett P, Rey JW, Hayee BH, Despott E, Murino A, Moreea S, Boger P, Dunn J, Mainie I, Graham D, Mullady DK, Early DS, Ragunath K, Anderson JT, Bhandari P, Goetz M, Kiesslich R, Coron E, Lovat LB, Haidry R. Hemostatic spray powder TC-325 in the primary endoscopic treatment of peptic ulcer-related bleeding: multicenter international registry. *Endoscopy* 2021; **53**: 36-43 [PMID: 32459000 DOI: 10.1055/a-1186-5360]

26 **Wedi E**, Fischer A, Hochberger J, Jung C, Orkut S, Richter-Schrag HJ. Multicenter evaluation of first-line endoscopic treatment with the OTSC in acute non-variceal upper gastrointestinal bleeding and comparison with the Rockall cohort: the FLETRock study. *Surg Endosc* 2018; **32**: 307-314 [PMID: 28656336 DOI: 10.1007/s00464-017-5678-7]

27 **Dango S**, Beißbarth T, Weiss E, Seif Amir Hosseini A, Raddatz D, Ellenrieder V, Lotz J, Ghadimi BM, Beham A. Relevance of surgery in patients with non-variceal upper gastrointestinal bleeding. *Langenbecks Arch Surg* 2017; **402**: 509-519 [PMID: 28091770 DOI: 10.1007/s00423-017-1552-2]

World Journal of Clinical Cases

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

World J Clin Cases 2024 December 16; 12(35): 6859-6863

DOI: 10.12998/wjcc.v12.i35.6859

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Role of high-dose amoxicillin dual therapy for *Helicobacter pylori* eradication in an Irish cohort: A prospective study

Raffaele Palmirotta, Concetta Cafiero, Marica Colella

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 C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade A, Grade C

Scientific Significance: Grade A, Grade B

P-Reviewer: El-Bendary M; Wang Y

Received: May 18, 2024

Revised: September 19, 2024

Accepted: October 9, 2024

Published online: December 16, 2024

Processing time: 158 Days and 16.8 Hours

Raffaele Palmirotta, Marica Colella, Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", Bari 70124, Italy

Concetta Cafiero, Area of Molecular Pathology, Anatomic Pathology Unit, Fabrizio Spaziani Hospital, Frosinone 03100, Italy

Corresponding author: Raffaele Palmirotta, MD, PhD, Associate Professor, Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", P.zza G. Cesare, 11, Bari 70124, Italy. raffaelepalmirotta@gmail.com

Abstract

Helicobacter pylori (*H. pylori*) infections may cause chronic gastritis, peptic ulcer disease, gastric cancers, and other conditions outside of the gastrointestinal tract. Hence, it is important to diagnose and treat it early. *H. pylori* is resistant to certain drugs in traditional eradication therapy, so alternative therapy protocols are needed, such as high-dose amoxicillin dual therapy (HDADT). This article aims to comment on a recent paper by Costigan *et al* in the *World Journal of Clinical Cases*. In this study, the authors recruited 139 patients diagnosed with *H. pylori*, all treated with HDADT. Of these, 93 were treatment-naïve and 46 had received at least one alternative treatment in the past. Four weeks after the end of the treatment, the urea breath test was administered to estimate the eradication rate. The total eradication rate was 56% (78/139), 62% for the treatment-naïve arm and 43% for the previous treatment arm, thus indicating a lower success rate for the arm that had previously received a different treatment regimen. In conclusion, a therapeutic approach with first-line HDADT may potentially be a better treatment, but the results are not sufficient to recommend the use of this regimen in a country with high levels of dual resistance.

Key Words: *Helicobacter pylori*; *Helicobacter pylori* eradication; High dose amoxicillin; High dose amoxicillin dual therapy; Triple therapy

Core Tip: Costigan *et al* conducted a prospective study to test high-dose amoxicillin dual therapy (HDADT) for *Helicobacter pylori* infections in an Irish cohort. Ireland is a high dual-resistance country for clarithromycin and metronidazole, so the traditional treatment does not work well. In addition, bismuth is not available in Ireland; therefore, the only recommended treatment is HDADT. The study considered in this editorial is the first to be conducted in Ireland, and it shows that HDADT does not always guarantee bacterial eradication.

Citation: Palmirotta R, Cafiero C, Colella M. Role of high-dose amoxicillin dual therapy for *Helicobacter pylori* eradication in an Irish cohort: A prospective study. *World J Clin Cases* 2024; 12(35): 6859-6863
URL: https://www.wjgnet.com/2307-8960/full/v12/i35/6859.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i35.6859

TO THE EDITOR

Helicobacter pylori (*H. pylori*) is currently recognized as the pathogenic agent of chronic gastritis, gastric and duodenal ulcers, gastric adenocarcinoma, and other types of cancers located in the gastrointestinal tract, *i.e.* mucosal associated lymphoid tissue lymphoma[1]. Actually, it is one of the most widespread bacterial infections worldwide[2,3].

In 1994, the World Health Organization recognized *H. pylori* as a class 1 carcinogen[4] and later in 2015, the Kyoto Consensus defined gastritis as an infectious disease, recommending early diagnosis followed by eradication therapy[5]. Over the years some guidelines for this kind of infection were generated. First in 1997, European guidelines suggested triple therapy, which consists of a combination of amoxicillin, proton pump inhibitors (PPIs), and either clarithromycin or metronidazole. However, the use of these antibiotics has allowed the pathogen to develop resistance; indeed, there are some areas considered "high resistance countries", where particularly resistant bacterial strains are present. Therefore, it is necessary to evaluate the right treatment before starting therapy to avoid the risk of failure.

In 2021, the European *H. pylori* Study Group and Consensus Panel released the Maastricht VI/Florence consensus report for the treatment of *H. pylori*. It recommends quadruple therapy (with bismuth or levofloxacin) in high-resistance countries, including Ireland, which has a dual resistance rate of over 15% for both clarithromycin and metronidazole.

In Ireland, bismuth is not available and combination tablets are not an option. In addition, fluoroquinolones are not used because of related adverse reactions[6]. Therefore, it is clear that Ireland requires an efficacious alternative therapeutic approach; for example, a possible second-line or rescue treatment is high-dose amoxicillin dual therapy (HDADT) or rifabutin triple therapy[7]. However, HDADT in naïve patients would be more favorable because it represents a simpler regimen therapy than triple or quadruple therapy. In a recent study, Costigan *et al*[8] sought to determine the effectiveness of HDADT in *H. pylori* infections in an Irish cohort. This editorial aims to comment on their findings.

USE OF HDADT

The study by Costigan *et al*[8] was prospective, open label, and carried out in Ireland in tertiary referral centers. The inclusion criteria were as follows: Patients aged 18 years or older, positive urea breath test (UBT), or positive endoscopy. The exclusion criteria included patients with allergies to penicillin, even if suspected, as well as those who refused to consent or to follow up after eradication.

A total of 187 patients were recruited for the study, of whom 139 were included in the analysis as they met all the inclusion criteria. Out of them, 76 were female (55%) and the mean age was 44.6 years (with a range of 19-83 years).

The 139 patients were divided into two groups: 93 (67%) received HDADT as their first-line therapy, while the other 46 (33%) received an alternative therapy before HDADT. The latter group comprised three subgroups: 32 patients received triple clarithromycin therapy before HDADT, 10 received two prior therapies and four had previously received three or more therapies.

The HDADT treatment is a 14-day course of amoxicillin (1 g three times a day) and esomeprazole (40 mg two times a day). After treatment, the researchers spoke to patients by phone to assess any side effects and to check how well they were complying with the treatment. Four weeks after therapy, the patients had another UBT test to check whether the *H. pylori* had been eradicated. They had to avoid taking PPIs for seven days, antibiotics for 28 days, and food for six hours before the test. The study results show that 78 patients (56%) had complete eradication based on negative post-treatment UBTs. In particular, in the group of patients with prior treatment, 20 out of 46 patients (43%) succeeded in eradicating the pathogen, compared to the first group where 58 patients out of 96 (62%) eradicated it.

Only 10 patients reported side effects, including nausea (10/10), and diarrhea (3/10), and the self-reported compliance was approximately 97%.

The results of the study suggest that first-line treatment seems to have a higher eradication success rate, although it is still below 90%. HDADT also seems to have some advantages in terms of cost and compliance, but its efficacy is too low to be considered first-line therapy. HDADT also appears to have some advantages in terms of cost and compliance, but its efficacy is still too low to be considered first-line therapy.

Unfortunately, this study has some limitations, such as the low number of participants; it is an open-label trial, but it can be considered a pilot study, which is useful for future research. For example, PCR and Epsilometer test (E-test) could be useful to define the pathogen and its resistance to the most used antibiotics, respectively.

Indeed, the management of *H. pylori* infection has undergone significant developments in line with the assessment of antibiotic resistance. This is commonly evaluated through the E-test, a culture-based method that is useful for determining the minimum inhibitory concentration (MIC) of antibiotics. Additionally, molecular techniques such as PCR have been employed to enhance diagnostic accuracy and treatment efficacy[9]. Both methods offer distinctive advantages in identifying infections and antibiotic resistance, which are pivotal for effective management.

A recent retrospective study of 1050 dyspeptic patients diagnosed with *H. pylori* infection showed that antimicrobial susceptibility testing (AST) using the E-test and subsequent tailored antibiotic therapy before first or second treatment had higher eradication rates (83.9% *vs* 73.8%, $P = 0.01$) and (77.3% *vs* 65.6%, $P = 0.27$), respectively, than those without AST[10].

Furthermore, the study demonstrates that the E-test is particularly advantageous in regions characterized by high resistance rates. This enables the implementation of prompt modifications to treatment regimens by susceptibility profiles. Additionally, it facilitates the management of *H. pylori* infection by enabling clinicians to prescribe antibiotic therapy with greater precision, particularly in cases of treatment failure[10].

However, although the E-test is a valuable tool in the management of *H. pylori*, it is essential to remain cautious about its limitations, particularly with regard to metronidazole resistance, for which further confirmation may be required[11].

Molecular methods such as PCR are highly sensitive for detecting *H. pylori* in different types of samples such as gastric juice, gastric biopsies, feces, and saliva. Antibiotic resistance can also be determined by amplification of resistance-associated genes using real-time PCR or by using nucleic acid sequencing methods[12].

In a retrospective study on 192 patients, PCR was correlated to improved eradication rates, with a notable increase in success from 62.2% to 73% after implementing new treatment. The cost-effectiveness of PCR alone was superior compared to culture methods, making it a preferred diagnostic strategy. The study therefore highlighted the cost-effective role of PCR in detecting *H. pylori* and monitoring antibiotic resistance, improving eradication success compared to using the E-test method alone[13].

In a recent study to evaluate the efficacy of real-time PCR assays in identifying *H. pylori* infection and antibiotic resistance in stool samples from 115 patients, the authors demonstrated 99.1% sensitivity and 100% specificity of the method and the ability to effectively assess clarithromycin/Levofloxacin resistance, enhancing tailored eradication treatments without endoscopy and indicating its potential in managing *H. pylori*[14].

Thus, it is evident that PCR and E-testing markedly enhance *H. pylori* management, as evidenced by a study comprising 288 patients with *H. pylori* infection. This study assessed the MIC of six antibiotic classes (metronidazole, clarithromycin, amoxicillin, tetracycline, levofloxacin, and rifampicin) using E-testing. Additionally, the resistance mutations in the rdxA, frxA, 23S rRNA, and gyrA genes of *H. pylori* were evaluated through PCR and targeted gene sequencing. The results therefore indicated that the combined use of these diagnostic methods makes it possible to optimize the selection of first-line and second-line treatment regimens by both preventing the development of resistance and reducing secondary resistance due to treatment failure[15].

On the other hand, the recently published Maastricht VI Consensus recommends routine susceptibility testing (molecular and culture) before prescribing first-line antibiotic treatment[16].

As personalized medicine approaches continue to develop, the pharmacokinetic and pharmacodynamic mechanisms will be better understood. We hope that genotypic analysis will be more accessible so that every patient will be able to take the right and effective dose of the drug, which surely will cause a positive effect[17].

CONCLUSION

Unfortunately, the results of the Costigan *et al*[8] study show that HDADT has limited efficacy as a first-line treatment in an area of high dual resistance. The results are not sufficient to recommend the use of the HDADT regimen in a country with high levels of dual resistance.

Over the last few years, the use of HDADT has increased, particularly in some Middle Eastern countries, to evaluate the efficacy in specific patient groups (*i.e.* children, elderly, *etc.*). This therapeutic choice is for health economic reasons and for the progressive emergence of antibiotic resistance towards the drugs used in triple and quadruple (BCQT) therapy protocols, in particular clarithromycin and metronidazole. On the other hand, these studies allow us to consider HDADT as a first-line treatment in specific populations or in the case of limited economic resources, reserving BCQT as a second-line treatment[18,19].

In 2020, Öztürk *et al*[18] conducted a study on 150 Turkish patients with *H. pylori* infection to test the effectiveness of high-dose dual therapy as a first-line treatment for infection. All patients received a 14-day, high-dose dual therapy comprising rabeprazole (20 mg three times a day) and amoxicillin (1 g three times a day) for *H. pylori* eradication. *H. pylori* stool antigen tests were administered to all participants at least 4 weeks after the completion of the treatment to assess eradication. The high-dose dual therapy demonstrated a 91.3% eradication rate of *H. pylori* infection. Per-protocol success was 94.4% among female patients ($n = 51$) and 89.6% among male patients ($n = 86$); in terms of sex, the differences were not significant ($P = 0.310$). Thus, the authors conclude that high-dose dual therapy with rabeprazole and amoxicillin is highly effective and well tolerated as first-line therapy for *H. pylori* eradication[18].

Similarly, in a more recent randomized controlled trial conducted by Yang *et al*[19] in 2023 on 150 Chinese patients, the authors concluded that 14 days of high-dose dual therapy (pantoprazole 40 mg 3 times daily and amoxicillin 1000 mg 3

times daily for 14 days) had a similar eradication rate as BQT but with fewer side effects, which may be better for elderly patients.

Although HDADT seems to be somewhat effective in these studies, almost all of the studies are inconclusive because the population is very small, and, as mentioned above, no cultural or molecular assessments of antibiotic resistance are included in the protocols. Nevertheless, these studies represent an important basis for future analysis and clinical trials.

FOOTNOTES

Author contributions: Palmirotta R, Cafiero C and Colella M contributed to this paper; Palmirotta R designed the overall concept and outline of the manuscript; Palmirotta R and Colella M contributed to the discussion and design of the manuscript; Palmirotta R, Colella M and Cafiero C contributed to the writing, editing the manuscript, and review of the literature; All authors have read and approved the final manuscript.

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

Country of origin: Italy

ORCID number: Raffaele Palmirotta 0000-0002-9401-7377; Concetta Cafiero 0000-0002-1401-8020; Marica Colella 0000-0003-0806-4327.

S-Editor: Qu XL
L-Editor: Filipodia
P-Editor: Cai YX

REFERENCES

1 **Santacroce L**, Cagiano R, Del Prete R, Bottalico L, Sabatini R, Carlaio RG, Prejbeanu R, Vermesan H, Dragulescu SI, Vermesan D, Motoc A, Losacco T. Helicobacter pylori infection and gastric MALTomas: an up-to-date and therapy highlight. *Clin Ter* 2008; **159**: 457-462 [PMID: 19169609]

2 **FitzGerald R**, Smith SM. An Overview of Helicobacter pylori Infection. *Methods Mol Biol* 2021; **2283**: 1-14 [PMID: 33765303 DOI: 10.1007/978-1-0716-1302-3_1]

3 **Zullo A**, Hassan C, Ridola L, Repici A, Manta R, Andriani A. Gastric MALT lymphoma: old and new insights. *Ann Gastroenterol* 2014; **27**: 27-33 [PMID: 24714739]

4 **World Health Organization**. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 60. 1994; 1-241. Available from: https://publications.iarc.fr/78

5 **Sugano K**, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P; faculty members of Kyoto Global Consensus Conference. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut* 2015; **64**: 1353-1367 [PMID: 26187502 DOI: 10.1136/gutjnl-2015-309252]

6 **HPRA Drug Safety Newsletter**. Fluoroquinolone antibiotics-EU review advises restrictions for certain infections and warns of rare but serious long lasting adverse reactions. Available from: https://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-91.pdf?sfvrsn=7

7 **Chey WD**, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *Am J Gastroenterol* 2017; **112**: 212-239 [PMID: 28071659 DOI: 10.1038/ajg.2016.563]

8 **Costigan C**, O'Sullivan AM, O'Connell J, Sengupta S, Butler T, Molloy S, O'Hara FJ, Ryan B, Breslin N, O'Donnell S, O'Connor A, Smith S, McNamara D. Helicobacter pylori: High dose amoxicillin does not improve primary or secondary eradication rates in an Irish cohort. *World J Clin Cases* 2024; **12**: 2773-2779 [PMID: 38899284 DOI: 10.12998/wjcc.v12.i16.2773]

9 **Medakina I**, Tsapkova L, Polyakova V, Nikolaev S, Yanova T, Dekhnich N, Khatkov I, Bordin D, Bodunova N. Helicobacter pylori Antibiotic Resistance: Molecular Basis and Diagnostic Methods. *Int J Mol Sci* 2023; **24** [PMID: 37298385 DOI: 10.3390/ijms24119433]

10 **Aumpan N**, Issariyakulkarn N, Mahachai V, Graham D, Yamaoka Y, Vilaichone RK. Management of Helicobacter pylori treatment failures: A large population-based study (HP treatment failures trial). *PLoS One* 2023; **18**: e0294403 [PMID: 38033026 DOI: 10.1371/journal.pone.0294403]

11 **Miftahussurur M**, Fauzia KA, Nusi IA, Setiawan PB, Syam AF, Waskito LA, Doohan D, Ratnasari N, Khomsan A, Adnyana IK, Akada J, Yamaoka Y. E-test versus agar dilution for antibiotic susceptibility testing of Helicobacter pylori: a comparison study. *BMC Res Notes* 2020; **13**: 22 [PMID: 31924273 DOI: 10.1186/s13104-019-4877-9]

12 **Aumpan N**, Mahachai V, Vilaichone RK. Management of Helicobacter pylori infection. *JGH Open* 2023; **7**: 3-15 [PMID: 36660052 DOI: 10.1002/jgh3.12843]

13 **Gallardo Padilla M**, León Falconi JL, Sánchez-Nebreda Arias R, Gómez Santos C, Muñoz Egea MDC, Orden Izquierdo E. Impact of the use of molecular techniques (PCR) on detection and eradication success against Helicobacter pylori. *An Pediatr (Engl Ed)* 2022; **96**: 190-195 [PMID: 35210193 DOI: 10.1016/j.anpede.2022.02.001]

14 **Fan CJ**, Li Z, Zhai LL, Wang H, Zhao XL, Xie DL, Cai Y, Huang K, Bai QX, Ding HO, Cheng JP. Diagnostic accuracy of a real-time PCR assay for detection of Helicobacter pylori and resistance to clarithromycin and levofloxacin directly from stool. *Eur Rev Med Pharmacol Sci*

2024; **28**: 3836-3840 [PMID: 38946381 DOI: 10.26355/eurrev_202406_36460]

15 **Hanafiah A**, Binmaeil H, Raja Ali RA, Mohamed Rose I, Lopes BS. Molecular characterization and prevalence of antibiotic resistance in Helicobacter pylori isolates in Kuala Lumpur, Malaysia. *Infect Drug Resist* 2019; **12**: 3051-3061 [PMID: 31632095 DOI: 10.2147/IDR.S219069]

16 **Malfertheiner P**, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, Gasbarrini A, Hunt RH, Leja M, O'Morain C, Rugge M, Suerbaum S, Tilg H, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study group. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. *Gut* 2022 [PMID: 35944925 DOI: 10.1136/gutjnl-2022-327745]

17 **Brittain HK**, Scott R, Thomas E. The rise of the genome and personalised medicine. *Clin Med (Lond)* 2017; **17**: 545-551 [PMID: 29196356 DOI: 10.7861/clinmedicine.17-6-545]

18 **Öztürk K**, Kurt Ö, Çelebi G, Şarlak H, Karakaya MF, Demirci H, Kılınç A, Uygun A. High-dose dual therapy is effective as first-line treatment for Helicobacter pylori infection. *Turk J Gastroenterol* 2020; **31**: 234-238 [PMID: 32343235 DOI: 10.5152/tjg.2020.18974]

19 **Yang Q**, He C, Hu Y, Hong J, Zhu Z, Xie Y, Shu X, Lu N, Zhu Y. 14-day pantoprazole- and amoxicillin-containing high-dose dual therapy for Helicobacter pylori eradication in elderly patients: A prospective, randomized controlled trial. *Front Pharmacol* 2023; **14**: 1096103 [PMID: 36817141 DOI: 10.3389/fphar.2023.1096103]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com