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ABOUT COVER

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AIMS AND SCOPE

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EDITORIAL

Diagnostic challenges from conflicting results of tests and imaging

Run Yu

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Abstract

Accurate diagnosis is the foundation of clinical care but accurate diagnosis is not easily reached in some cases. In rare instances, even a sophisticated multidisciplinary team at an academic medical center cannot reliably reach an accurate diagnosis after extensive testing and imaging, and has to wait until histological diagnosis or even autopsy results are available. The underlying reason of challenging diagnoses is mostly conflicting data from history, tests, and imaging that point to different diagnoses. In this issue of *World Journal of Clinical Cases*, Huffaker *et al* reported such a challenging case of a tricuspid mass in a patient with Li-Fraumeni syndrome. The case by Huffaker *et al* powerfully illustrates the occasional diagnostic challenges inherent in our current diagnostic approach and the current technology. Clinicians should realize that in rare situations, agnosticism in diagnosis is unavoidable but a treatment has to be initiated so long as the principle of *primum non nocere* is upheld.

Key Words: Li-Fraumeni syndrome; Cardiac mass; Thrombus; Challenging diagnosis; Histological diagnosis; False positive results

Core Tip: The underlying reason of challenging diagnoses is mostly conflicting data from history, tests, and imaging that point to different diagnoses. The case by Huffaker *et al* powerfully illustrates the occasional diagnostic challenges inherent in our current diagnostic approach and technology. Clinicians should realize that in rare situations, agnosticism in diagnosis is unavoidable but a treatment has to be initiated so long as the principle of *primum non nocere* is upheld.

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INTRODUCTION

Accurate diagnosis is the foundation of clinical care but accurate diagnosis is not easily reached in some cases. In rare instances, even a sophisticated multidisciplinary team at an academic medical center cannot reliably reach an accurate diagnosis after extensive testing and imaging, and has to wait until histological diagnosis or even autopsy results are available. The underlying reasons of challenging diagnoses fall into two categories: Much more commonly, conflicting data from history, tests, and imaging that point to different diagnoses, and less commonly, failure to recognize a potential novel disease[1].

CONFLICTING DIAGNOSTIC RESULTS

Conflicting results from tests and imaging are quite common in clinical practice; most experienced clinicians are well versed in teasing out common conflicting results from tests and imaging. For example, normal hemoglobin A1c in a patient with history of poorly controlled diabetes and severe hyperglycemia who has just received blood transfusion is well recognized as a false negative result due to transfusion. As the disease becomes rarer, specialists need to be called upon to interpret conflicting results. For example, pancreastatin and chromogranin A, both markers of neuroendocrine tumor, may be much elevated and normal, respectively, but elevated pancreastatin can be false positive due to spurious test method[2]. Our experience with imaging follows the same pattern. It is well known that renal cell carcinoma can have normal fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) so that a normal FDG uptake cannot rule out the cancer. When dodecane tetraacetic acid octreotate (DOTATATE)-PET first became available, uptake at the pancreatic head/neck region without computed tomography (CT) correlates often was thought as evidence of pancreatic neuroendocrine tumor. Accumulating experience and research over the years now show that the DOTATATE uptake at the pancreatic head/neck region is most often due to pancreatic polypeptide cell pseudohyperplasia[3]. Thus at academic centers, multidisciplinary teams of experts from various specialties usually can reach a correct diagnosis based on history, laboratory tests, and imaging, before histological evidence is required. Once in a while, even a team of experts cannot reliably make an accurate diagnosis.

AN ILLUSTRATIVE CASE

In this issue of World Journal of Clinical Cases, Huffaker *et al*[4] reported such a challenging case of a tricuspid mass in a patient with Li-Fraumeni syndrome (LFS). LFS is an autosomal dominant disease of multiple malignancies due to inactivating mutations of tumor suppressor P53. Common malignancies in LFS include soft tissue sarcoma, osteosarcoma, and breast cancer. The 30-year-old female described by Huffaker *et al*[4] had clearly diagnosed LFS with history of multiple LFS-defining malignancies. She also had two atrial septal defects so underwent periodic echocardiogram for signs of right heart enlargement. The latest transthoracic echocardiogram showed a 1-cm mass on the tricuspid valve, which had not been present a year before. Clinically she was well and exhibited no cardiac signs or symptoms.

The differential diagnosis of a cardiac mass includes tumor, thrombus, and vegetation[5]. To pinpoint the diagnosis without histology is often challenging. Clinical history and imaging characteristics of the mass are helpful predictors of a diagnosis. For example, a left ventricular mass in a patient with embolic stroke and reduced left ventricular wall motion is most likely a thrombus[6]. In this young female with LFS, tumor was a concern as cardiac sarcoma has been reported in LFS[7]. The patient was also at high risk of thrombus due to hypercoagulability associated with extensive malignancy history. The case report did not specify whether the patient was taking oral contraceptives or other hormonal therapies, which has been associated with tricuspid thrombus presumably due to hormonally-related hypercoagulability[8]. As she overall felt well and presumably did not have fever or anemia, vegetation was highly unlikely and could be ruled out clinically. There are no laboratory tests to differentiate a cardiac tumor from a thrombus; detailed imaging is needed to further characterize the tricuspid mass. Transesophageal echocardiogram describes the location, shape, and motion of a cardiac mass in real time but does not particularly tell the nature of the mass. In this case, transesophageal echocardiogram showed that the mass was attached to the anterior tricuspid valve leaflet, presumably without abnormal blood flow through the right heart. Magnetic resonance imaging (MRI) is the most commonly used imaging modality to differentiate a cardiac tumor from a thrombus with the late gadolinium enhancement protocol based on the reasonable assumption that a thrombus should not have significant blood supply[9]. In this case, gadolinium enhancement was noted on the tricuspid mass, which was interpreted as imaging evidence of tumor. Could the authors use additional imaging? FDG-PET/CT has been used to differentiate a cardiac tumor from a thrombus but it has also been subject to falsely suggesting malignancy in a case of organized thrombus[10].

In a challenging case like this one, the next critical question is whether making an accurate diagnosis (*i.e.*, a tricuspid tumor *vs* thrombus) affects management? A tricuspid tumor would require surgical resection but a tricuspid thrombus could potentially be treated with anticoagulation. Anticoagulation, however, is associated with risk of embolism, and in this case, pulmonary embolism, which is a serious adverse effect[11]. The authors opted to stop at the MRI and proceeded with surgical resection, regardless whether this was a tricuspid tumor or thrombus. The histology showed that the tricuspid mass was actually an organized thrombus.

CONCLUSION

The case by Huffaker *et al*[4] powerfully illustrates the occasional diagnostic challenges inherent in our current diagnostic approach and the current technology. Clinicians should realize that in rare situations, agnosticism in diagnosis is unavoidable and an accurate diagnosis simply cannot be made, but a treatment has to be initiated so long as the principle of *primum non nocere* is upheld. Technological advances such as radiomics and artificial intelligence may aid us achieving a more accurate diagnosis[12,13].

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EDITORIAL

Are case reports valuable? Exploring their role in evidence based medicine and patient care

Tarun Kumar Suvvari

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Abstract

Case reports, often overlooked in evidence-based medicine (EBM), play a pivotal role in healthcare research. They provide unique insights into rare conditions, novel treatments, and adverse effects, serving as valuable educational tools and generating new hypothesis. Despite their limitations in generalizability, case reports contribute significantly to evidence-based practice by offering detailed clinical information and fostering critical thinking among healthcare professionals. By acknowledging their limitations and adhering to reporting guidelines, case reports can contribute significantly to medical knowledge and patient care within the evolving landscape of EBM. This editorial explores the intrinsic value of case reports in EBM and patient care.

Key Words: Clinical cases; Case reports; Evidence based medicine; Editorial; Healthcare research

Core Tip: Case reports are indispensable in evidence-based medicine, offering crucial insights into rare cases and innovative treatments. While they are not as robust as randomized controlled trials or observational studies, case reports provide essential information that can guide clinical decision-making and stimulate further research. Embracing the significance of case reports can enrich medical education and improve patient outcomes.

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INTRODUCTION

Case reports have historically played a vital role in medical research, with examples like Louis Pasteur's work on the rabies vaccine and Sigmund Freud's studies on hysteria[1]. In present scenario, case reports also play a crucial role in evidence-based medicine (EBM) and patient care by providing valuable insights into novel aspects of diseases, therapies, and adverse effects of treatments[2]. Despite being placed low on the evidence hierarchy, case reports are essential for signifying novel occurrences, generating hypotheses, and serving as the first-line evidence to test statistical methods[2]. They permit the discovery of new diseases, unexpected clinical scenarios and pathophysiology, contributing to medical education and the study of rare conditions that may not be feasible to study in large-scale trials[3]. Additionally, case reports can provide a narrative that complements quantitative data, offering a more holistic view of patient care and outcomes[4].

Case reports have traditionally been a cornerstone of medical literature, providing valuable insights into rare conditions, unusual presentations, and treatment outcomes. However, with the rise of EBM, there has been a debate on the relevance and role of case reports in modern medical practice. Proponents of EBM argue that case reports, due to their anecdotal nature and limited generalizability, are of lower quality evidence compared to systematic reviews and randomized controlled trials[5]. The emphasis on rigorous research methodologies and systematic reviews in EBM has led some to view case reports as outdated and potentially misleading[6].

Despite these criticisms, some scholars argue that case reports still hold value in the era of EBM. They suggest that while EBM emphasizes quantitative analysis and systematic reviews, there are aspects of clinical practice that resist such quantification, such as tacit knowledge and humanistic considerations[7].

Furthermore, case reports continue to be published in reputable medical journals, indicating ongoing interest and relevance in the medical community[3,4]. They offer a platform for sharing unique clinical experiences, innovative treatments, and unexpected complications that can contribute to medical knowledge and patient care[4]. While EBM remains a critical foundation for clinical decision-making, the integration of case reports alongside systematic reviews and clinical trials can enrich the evidence base and provide a more comprehensive understanding of complex medical scenarios[8].

IMPORTANCE OF CASE REPORTS

As a physician point of view, importance of case reports include:

Evidence generation

Well-written case reports contribute to evidence generation and clinical practice by offering valuable information to clinicians when other evidence is lacking[9].

Investigating new hypotheses

Case reports can stimulate further investigations, leading to the discovery of new diseases, therapeutic approaches, or indications for existing treatments[8,9].

Early detection of emerging diseases

In the early stages of a new or emerging disease, case reports are often the first source of information. They can help healthcare professionals recognize patterns, symptoms, and potential treatment strategies before large-scale studies are conducted[9,10]. For example, Kaposi's Sarcoma was published as a case series, stating that all the cases had in common homosexual practices, suggesting possible sexual transmission of an unknown infection which turned out to be as the first report of human immunodeficiency virus-acquired immunodeficiency syndrome[1,11]. Similarly, single cases of Influenza Virus, Ebola Virus, and SARS-CoV virus were initially reported, which eventually escalated into global outbreaks[1,12].

Rare or unusual cases

Case reports are particularly valuable when dealing with rare or unusual medical conditions. Since RCTs often focus on common diseases, case reports can shed light on atypical presentations, unusual complications, or rare side effects of treatments[4,6]. For instance, several genetic conditions like neurofibromatosis type 1, trisomy 18, and Wolf-Hirschhorn syndrome, were first identified and published as single case report[1,13].

Educational value

Case reports are beneficial tools in graduate medical education, helping students acquire clinical competencies and apply evidence-based thinking in practice-based learning[10,14].

LIMITATIONS OF CASE REPORTS

Small sample size

Due to their nature, case reports have a small sample size, limiting their ability to infer causality or calculate incidence or prevalence[4,15].

Generalizability concerns

Case reports lack generalizability and may not be representative of broader patient populations or clinical practices[4,16].

Retrospective design

Retrospective design may lead to missing relevant data not documented in medical records, affecting the completeness of the report[4].

EDUCATIONAL VALUE AND FUTURE PERSPECTIVES

Skill development

Writing case reports can enhance critical thinking, observational skills, medical writing abilities, and hypothesis generation for young doctors and medical students[14,17].

Patient-centered care

Case reports contribute to patient-centered care by highlighting unique cases, rare manifestations of diseases, and adverse effects of treatments[14,17].

Professional development

Engaging in case reporting can provide valuable experience with the editorial process, motivate scholarly views on clinical work, and improve understanding of patient-centered care[14,17].

DISCUSSION

Case reports serve as a platform for training medical students, residents, and fellows in scientific writing and critical thinking[17]. They enhance awareness of rare disorders, clarify new aspects of disease etiology, and describe treatment responses, contributing to better-informed healthcare professionals. By documenting new or innovative treatments, case reports can stimulate further investigations and the discovery of novel therapeutic approaches[14]. They provide a starting point for exploring potential interventions and outcomes. Case reports offer a structured approach to case-based learning in healthcare education. They facilitate the comparison of clinical scenarios, aiding in the evaluation, diagnosis, treatment, and prognosis of diseases[14,17].

While case reports may not provide generalizable results like larger studies, they offer detailed qualitative and quantitative clinical information on individual patients that can complement evidence from group studies[18]. This supplemental data can contribute to a more comprehensive understanding of disease management. Case reports help in sharing information about rare disorders that may not be investigated through controlled clinical trials due to their low incidence. They also play a crucial role in drug safety surveillance by documenting adverse effects promptly[18,19].

A dedicated issue to case reports would serve as a platform to share valuable clinical experiences[9]. This would not only facilitate the identification of rare pathologies and novel diseases but also shed light on atypical presentations of common ailments. Even seemingly unique or outlier cases can hold significant value for researchers and clinicians, potentially uncovering previously unrecognized drug interactions or subtle disease manifestations.

CONCLUSION

In conclusion, case reports still hold a valuable role in EBM, as they continue to offer valuable insights into rare conditions, treatment outcomes, and unexpected effects. Case reports play a crucial role in medical education, hypothesis generation, and contributing to the understanding of complex medical scenarios. While systematic reviews and randomized controlled trials are prioritized in evidence hierarchy, case reports provide a narrative perspective that complements quantitative data, enriching the evidence base and enhancing patient care. Acknowledging the unique value of case reports alongside other forms of evidence can lead to a more comprehensive understanding of patient care and

outcomes.

FOOTNOTES

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Recent advances in managing obstructive sleep apnea

Deb Sanjay Nag, Abhishek Chatterjee, Roushan Patel, Biswajit Sen, Bappa Ditya Pal, Gunjan Wadhwa

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Abstract

Obstructive sleep apnea (OSA) is a rapidly increasing global concern. If it remains untreated, it can lead to cardiovascular, metabolic, and psychiatric complications and may result in premature death. The efficient and effective management of OSA can have a beneficial effect and help reduce the financial burden on the health sector. There has been constant development in OSA management, and numerous options are available. The mainstay of therapy is still the conventional measures and behavioral modifications. However, in cases of failure of these modalities, surgical therapy is the only option. Numerous studies have shown that proper management of OSA has beneficial effects with good long-term outcomes.

Key Words: Sleep apnea; Obstructive; Continuous positive airway pressure; Concepts; Pharmacological

Core Tip: Obstructive sleep apnea (OSA) is a common sleep disorder that is responsible for not only its symptoms but is also a causative disorder for many chronic and morbid diseases like hypertension, diabetes, and metabolic disorders. While patients with OSA have various treatment options with varied success, conservative modalities, airway pressure devices, pharmacologic modalities, and surgical options must be customized based on individual patient needs.

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INTRODUCTION

The term "Apnea" is a Greek word that means "without breath." Obstructive sleep apnea was described for the first time in 1837 by Charles Dickens[1], who described it as "Pickwickian syndrome." However, in 1956, Sydney Burwell described the signs and symptoms of this condition in detail and distinguished this condition from other diseases[2]. Apnea is a discontinuance of airflow during sleep, which has to last for at least 10 seconds with oxygen desaturation of more than 3% with or without associated arousal[3]. Intermittent complete or partial upper airway obstruction OSA is defined as the occurrence of at least five hypo-apneas or apneas in an hour, which decreases oxygen saturation and sleep fragmentation [3].

OSA presents a global burden and affects almost 10% of the population[4], with 14% prevalence among males and 5% in females[4]. The prevalence of OSA is 47%-67% after menopause, and an increase in body weight is not the only factor responsible for this[5].

Several authors have found a strong correlation between OSA and the development of hypertension, stroke, coronary artery disease, congestive heart failure, diabetes mellitus, and metabolic syndrome[6,7]. OSA is also associated with daytime somnolence[8], depression[9], cognitive decline[10] and may also lead to motor vehicle accidents[11]. Therefore, OSA should be diagnosed early and managed efficiently and adequately to avoid significant economic costs to the healthcare system.

MANAGEMENT OF OSA

The management of OSA can be sub-stratified into conservative measures, including weight loss, exercise, positional therapy, and alcohol avoidance.

Weight loss

Body mass index has been considered an important predictor of OSA, and studies[11] have shown that a reduction of 10% in body weight can reduce the apnea and hypopnoea index by 26%. Reduction in body weight also decreases the collapsibility of the airway and results in near-complete resolution of apnea[12]. However, the effect of bariatric surgery on the management of OSA is controversial. Some studies[13,14] have shown beneficial effects, whereas some studies[15] have failed to observe any favorable effects. A systematic review and meta-analysis of 136 studies of 22094 patients showed that effective weight loss resulted in "complete resolution or improvement" in OSA[13].

Exercise

Physical exercise is recommended in patients suffering from OSA because it significantly decreases the cardiovascular complications associated with OSA. Authors of the AHEAD (Action for Health in Diabetes) study[15] observed the beneficial effects of lifestyle interventions, including exercise, on OSA. A 10-year follow-up of 134 adults with polysomnography showed that weight loss through intensive lifestyle intervention improved OSA severity[16].

Positional sleep therapy

The mainstay of positional sleep therapy is to encourage patients with OSA to sleep on their side rather than sleeping in the supine position. To keep the patients off their backs at night, various devices and garments are used in positional sleep therapy. Vibratory sleep devices raise a vibratory alarm when placed around the neck at night, and the patient rolls over to a supine position. The vibration stops when the patient rolls out of the supine position. A Cochrane Database Systematic Review, which included 8 studies and 323 patients, showed that positional sleep therapy was significantly less effective as compared to continuous positive airway pressure (CPAP) in reducing apnea-hypopnea index (AHI)[17]. However, it was tolerated longer than CPAP at night[17].

Alcohol avoidance

A meta-analysis[18] has shown that not only do people consuming alcohol have a 25% higher prevalence of obstructive sleep apnea, but they also have a longer duration of apnea and a lower nadir of oxygen saturation[19]. The authors have concluded that these effects were due to the selective adverse effect on airway dilator muscles with depression of genioglossus muscle activity or on the hypoglossal nerve[20,21]. A systematic review and meta-analysis of 21 studies from 1985 to 2015 concluded that the "risk of OSA to be increased by 25%" in those who consumed alcohol or consumed it in higher amounts as compared to those who did not consume it in lower amounts[18].

AIRWAY PRESSURE TREATMENTS

CPAP

This is the most common mode of administration of positive airway pressure in the management of OSA. In this mode, a positive pressure is maintained throughout the respiratory cycle. CPAP machines deliver a continuous flow of pressurized air to help keep the upper airway patent; thus, they help reduce AHI significantly[21]. In a meta-analysis[21], CPAP has been considered as the first line of treatment for moderate-to-severe OSA and for mild obstructive sleep apnea with cardiovascular disease or excessive daytime somnolence. CPAP should be used for at least 4 hours on 70% of nights recommended for use during the entire sleep period[21]. The common adverse effects of using CPAP in OSA patients are nasal irritation, dry mouth, and infection of the sinuses[21]. The m but is-analyses commissioned by the American Academy of Sleep Medicine evaluated 184 studies and concluded that positive airway pressures resulted in significant clinical improvement in disease severity and "sleep-related quality of life in adults"[21].

Nasal expiratory airway pressure

Devices have been used as an alternative to CPAP devices in mild to moderate OSA[22]. In contrast to CPAP, these devices only generate resistance to expiratory airflow while providing minimal inspiratory resistance[22]. In a randomized trial involving a "cohort of 34 analyzable subjects" where these devices were compared to placebo treatment, the median AHI of the subjects reduced from 15.7 events per hour to 4.1 events per hour[23]. Discomfort during exhalation, nasal irritation, and dry mouth are the common adverse effects of using these nasal devices[22].

Intraoral negative pressure therapy

The United States Food and Drug Administration (FDA) has recently approved this therapy for sleep apnea of any variety[23]. These devices apply negative pressure through an intraoral device held in place by a flange between teeth and lips. Studies[23] have shown that compared to retroglossal airway collapse, these devices are more effective when OSA is due to retropalatal collapse[23]. In a study that enrolled 19 patients, 15 were responders, and 4 were non-responders to therapy with a negative pressure with an intraoral interface[24].

Mid-frequency anti-snoring devices

This device is usually worn in the lower jaw (submandibular area) when a patient lies supine and sleeps. The device delivers a mid-frequency electrical stimulus when the patient starts snoring. In a recently concluded study[25] on 50 patients, the mid-frequency anti-snoring device successfully decreased the duration of snoring, AHI episodes, and SpO2 < 90% in moderate-to-severe OSA patients.

Pharmacological agents

Studies[22] have shown that protriptyline and fluoxetine reduced the number of apnea and hypopnea events by reducing rapid eye movement sleep. Carbonic anhydrase inhibitors like topiramate, acetazolamideor zonisamide, also reduce the adverse impact on AHI[22]. In a "prospective crossover unblinded trial" on 12 patients, 6 had good responses to either fluoxetine or protriptyline, and fluoxetine was better tolerated than protriptyline[26].

Surgical

Surgical options to OSA patients should be offered only when conservative measures and airway devices have failed to provide any benefits to these patients[20]. The surgical procedures offered to these patients are:

Uvulopalatopharyngoplasty

This procedure has been the mainstay of surgical treatment since 1980 when Fujita *et al*[27] described it for the first time. A meta-analysis of 15 observational studies showed that the AHI could be reduced by 33%[28]. However, the same meta-analysis[28] showed that laser-assisted uvulopalatopharyngoplasty could reduce the incidence of AHI by only 17%. Adverse effects of this surgery include postoperative hemorrhage, difficulty in swallowing or nasal regurgitation, voice changes, disturbance of taste, and even death in 0.2% of the operated cases[28].

Tongue reduction surgery

Midline glossectomy with removing elliptical tongue tissue from the dorsal surface has been proposed as an adjunct to uvulopalatopharyngoplasty[22]. Radiofrequency ablation and reduction of tongue size were associated with a decrease in AHI by 34%[27]. In a study on 45 patients of moderate-to-severe OSA AHI reduction of > 50% was achieved in 75% of patients undergoing transoral robotic surgery (TORS) and 62.1% in patients undergoing tongue base coblation resection [29]. Patients undergoing TORS have less incidence of postoperative hemorrhage foreign body sensation of dysfunction in taste perceptio[29].

Hypoglossal nerve stimulation

The FDA approved hypoglossal nerve stimulation[22] in 2014; since then, it has been gaining popularity. The hypoglossal nerve stimulator device has an implantable pulse generator, a lead for stimulation, and a lead for sensing respiration. The pulse generator senses and, if needed, then enhances the neural stimulation of the hypoglossal nerve to the genioglossus and geniohyoid muscles. Thus it results in protrusion of the tongue forward. In the first such report of a 5-year follow-up surgical intervention for OSA using "upper airway stimulation *via* a unilateral hypoglossal nerve implant" on 97 patients

Table 1 Treatment modalities of obstructive sleep apnea

Broad modalities	Specific modalities	Evidence
Conservative measures	Weight reduction	Moderate
	Exercise	Moderate
	Positional sleep therapy	Moderate
	Alcohol avoidance	Moderate
Airway pressure treatments	Continuous positive airway pressure	High (Gold standard)
	Nasal expiratory airway pressure devices	Moderate
	Intraoral negative pressure therapy	Moderate-low
Pharmacological therapy	Antidepressants, carbonic anhydrase inhibitors	Very low
Surgical procedures	Uvulopalatopharyngoplasty	Moderate-low
	Tongue size reduction	Moderate-low
	Hypoglossal nerve stimulation	Moderate-low
	Maxillomandibular advancement	Moderate-low

who completed the protocol, significant improvement in quality of life and Epworth Sleepiness Scale was observed in 15%-67% and 33%-78% respectively), with significant AHI improvements being observed on 75% of 71 participants who volunteered for polysomnography[30].

Maxillomandibular advancement

A composite procedure consisting of Lefort 1 osteotomy and bilateral sagittal split of mandibular rami increases airway volume by creating a larger space[22]. A Case series involving 214 such cases has shown that this surgery resulted in an 87% decrease in AHI[28].

CONCLUSION

OSA, although a commonly encountered problem, can be managed efficiently. Various existing and evolving treatment modalities (Table 1: Treatment modalities of obstructive sleep apnea) include conservative measures, airway pressure treatments, pharmacological therapy, and surgical procedures. The Grading of Recommendations Assessment, Development, and Evaluation approach has been used to provide the quality of currently available evidence for each therapeutic modality[31]. All have demonstrated varied degrees of success, and further search will guide us toward patient-specific treatment modalities. However, CPAP remains the gold standard of treatment as of date. It is also highly cost-effective, especially after 1-2 years of continuous therapy, given its impact on quality of life, incidence of cardiovascular diseases, and motor vehicle accidents[32,33].

FOOTNOTES

Author contributions: Nag DS, Chatterjee A, Patel R, Sen B, Pal BD, Wadhwa G contributed to this paper; Nag DS and Chatterjee A designed the overall concept and outline of the manuscript; Chatterjee A, Sen B, Patel R, Pal BD contributed to the discussion and design of the manuscript; Nag DS, Chatterjee A, Patel R, Sen B, Pal BD, Wadhwa G contributed to the writing, and editing the manuscript and review of literature.

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EDITORIAL

Importance of risk assessment, endoscopic hemostasis, and recent advancements in the management of acute non-variceal upper gastrointestinal bleeding

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Abstract

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) is a common medical emergency in clinical practice. While the incidence has significantly reduced, the mortality rates have not undergone a similar reduction in the last few decades, thus presenting a significant challenge. This editorial outlines the key causes and risk factors of ANVUGIB and explores the current standards and recent updates in risk assessment scoring systems for predicting mortality and endoscopic treatments for achieving hemostasis. Since ANUVGIB predominantly affects the elderly population, the impact of comorbidities may be responsible for the poor outcomes. A thorough drug history is important due to the increasing use of antiplatelet agents and anticoagulants in the elderly. Early risk stratification plays a crucial role in deciding the line of management and predicting mortality. Emerging scoring systems such as the ABC (age, blood tests, co-morbidities) score show promise in predicting mortality and guiding clinical decisions. While conventional endoscopic therapies remain cornerstone approaches, novel techniques like hemostatic powders and over-the-scope clips offer promising alternatives, particularly in cases refractory to traditional modalities. By integrating validated scoring systems and leveraging novel therapeutic modalities, clinicians can enhance patient care and mitigate the substantial morbidity

and mortality associated with ANVUGIB.

Key Words: Non-variceal upper gastrointestinal bleeding; Upper gastrointestinal bleeding; Gastrointestinal bleeding; Risk stratification; Risk assessment scores; Prognostication; Endoscopy; Esophagogastroduodenoscopy; Endoscopic hemostasis

Core Tip: Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) presents a significant medical challenge. Despite advancements in management, mortality remains high in the context of an increasingly elderly, comorbid population. While early risk stratification using established scoring systems ensures targeted management, newer scoring systems show promise in predicting mortality and should be integrated into medical practice after proper validation. Novel endoscopic techniques offer promising alternatives, especially in cases where conventional modalities are ineffective. By integrating validated scoring systems and adopting innovative therapeutic modalities, clinicians can enhance patient care and mitigate the substantial mortality associated with ANVUGIB.

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INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB), defined as any bleeding originating above the ligament of Treitz in the duodenum, is a medical emergency commonly encountered in clinical practice[1,2]. According to their etiology, upper gastrointestinal hemorrhage is further subdivided into variceal and non-variceal UGIB (NVUGIB). Acute non-variceal UGIB (ANVUGIB) has an annual incidence of 67 *per* 100000 individuals and accounts for 80% of all cases of UGIB[3,4]. In the recent issue of the *World Journal of Clinical Cases*, we read with interest an article that elucidated the clinical characteristics of ANVUGIB by retrospectively analyzing patient data from a tertiary-care hospital in China[5]. The high mortality rates and the effectiveness of endoscopic hemostasis in the management of ANVUGIB particularly piqued our interest. Despite the advances in diagnostic and treatment modalities, NVUGIB remains a common medical problem owing to its sudden onset and rapid progression, prevalence of risk factors such as cardiovascular disease, increasing use of blood-thinning medications (such as aspirin, anticoagulants, and antiplatelet agents) and non-steroidal anti-inflammatory drugs (NSAIDs), and high morbidity and mortality[6,7]. The current guidelines recommend esophagogastroduodenoscopy (EGD) as the procedure of choice for both the diagnosis and management of NVUGIB and transcatheter angiographic embolization or surgery in cases of refractory bleeding[8-11]. Various risk assessment scores, such as the Glasgow-Blatchford Score (GBS) and the Rockall score, are routinely used for risk stratification in UGIB and may have a role in predicting the risk of mortality due to re-bleeding[12]. Thus, risk stratification and endoscopic interventions are key tools in deciding the line of management and determining morbidity and mortality. This editorial reviews the current demographics, etiologies, and risk factors associated with ANVUGIB and highlights the crucial role of early risk stratification in reducing mortality and endoscopic therapies in achieving hemostasis. It also discusses the emerging scoring systems and novel endoscopic technologies that show promise in guiding clinical decisions and reducing mortality.

DEMOGRAPHICS, ETIOLOGIES, AND RISK FACTORS OF NVUGIB

Males are affected more compared to females, with the majority of patients being older than 65 years[13,14]. Peptic ulcer disease (PUD) is the most common cause of ANVUGIB, followed by upper gastrointestinal malignancy, Mallory-Weiss syndrome, and gastric angiodysplasia[4,13].

Significant advancements in medicine have caused a reduction in ulcer-related bleeding over time due to the decreased incidence of PUD itself[13]. However, the mortality rates have not changed much, owing to the impact of co-morbidities in an aging population[2]. Cardiovascular disease (congestive heart failure, ischemic heart disease) is the most frequent comorbidity encountered in such patients, followed by diabetes mellitus, chronic liver disease, and chronic kidney disease[13,14].

Besides co-morbidities, there are other factors that increase the chances of mortality from NVUGIB. Particular attention must be paid to the patient's drug history. NSAIDs and aspirin (acetyl-salicylic acid) are recognized risk factors for increasing the chance of bleeding from peptic ulcers and severe erosive gastritis[15]. These drugs can cause NVUGIB by reducing prostaglandins in the gastric mucosa and increasing the susceptibility to mucosal damage[16,17]. The use of anticoagulants and antiplatelet drugs in an aging population with multiple co-morbidities may be associated with an increased risk of bleeding in NVUGIB[17,18]. *Helicobacter pylori (H. pylori)* infection represents the single most common

cause of PUD, which is in turn the leading cause of NVUGIB[19]. *H. pylori* status should be assessed in cases of NVUGIB due to PUD and reassessed after four weeks if the results are negative[10]. Yin and Yu[17] described a risk prediction model and concluded six independent risk factors for NVUGIB by analyzing two years' worth of clinical data retrospectively[17]. The risk factors for NVUGIB are summarized in Table 1.

RISK ASSESSMENT SCORES AS PREDICTORS OF INTERVENTIONS AND MORTALITY

Following successful initial resuscitation, patients should be stratified as low- and high-risk using risk assessment scoring systems to ensure appropriate patient disposition. These scoring systems act as clinical prediction guides and can be used to predict the line of treatment and mortality[20]. Getting timely endoscopic hemostatic treatment is crucial for improving the chances of survival, especially in high-risk groups. Proper evaluation of the patient's hemodynamic status and accurate risk assessment can lead to successful treatments. This is why a highly efficient scoring system is needed to help predict the prognosis and guide appropriate management[21]. There are a variety of scoring systems, each with different goals, like assessing the type of intervention, mortality, length of hospital stay, need for blood transfusions, *etc*. Some utilize only clinical data (pre-endoscopy scoring systems), while others require additional endoscopic findings (post-endoscopy scoring systems)[22]. A compilation of scoring systems is provided in Table 2.

Some well-established pre-endoscopy scoring systems are the Glasgow-Blatchford Score (GBS), pre-endoscopic Rockall Score, and AIMS65 (albumin, international normalized ratio, mental status, systolic blood pressure, age ≥ 65 years) score [23-25]. Initially developed to predict the need for intervention, the GBS has been found to possess the highest accuracy in predicting the need for hospital-based intervention and mortality[26]. As such, guidelines recommend the use of GBS for risk stratification in UGIB and state that patients with GBS ≤ 1 have a low risk of mortality and can be managed as an outpatient[10,11,27].

The age, blood tests, co-morbidities (ABC) score and international bleeding score (INBS) are newly-developed pre-endoscopy scoring systems that can accurately predict the 30-day mortality in patients with NVUGIB[21,28]. The ABC score appeals as a clinical tool in terms of simplicity and ease of assessment at the bedside and has outperformed the traditional prognostic scores (which include scores like the GBS) in predicting mortality in patients with UGIB[29]. Studies have shown that the ABC score works better on younger patients compared to older patients[29]. The INBS is a novel prognostic score that is computed using medical history and biochemical results. It has been found to be superior to the traditional scoring systems in predicting mortality and can estimate the chances of re-bleeding, endoscopic hemostasis failure, and the duration of hospitalization[21]. These scoring systems need validation from large-scale studies before they can be incorporated into clinical practice.

Since post-endoscopy scores require endoscopy findings, it may delay risk assessment in setups where endoscopy is the limiting factor in UGIB management. Early risk stratification allows for early identification of high-risk patients, thereby ensuring targeted management of low- and high-risk patients[11,27]. Therefore, much of the focus should be on pre-endoscopy scoring systems, which can be calculated soon after patient presentation. Pre-endoscopy scores like the ABC score and INBS can be useful as quick and effective tools in predicting the outcomes of ANVUGIB, shortening hospital stays, and guiding clinical decisions to reduce mortality by increasing the chances of successful endoscopic hemostasis.

ENDOSCOPIC INTERVENTIONS FOR ACHIEVING HEMOSTASIS

After initial resuscitation and hemodynamic stabilization, patients with UGIB should undergo endoscopy within 24 h of admission. Endoscopy is the procedure of choice for the diagnosis and management of ANVUGIB[8-11]. Current guidelines recommend early endoscopy (within 24 h) in both high- and low-risk patients since early endoscopies result in early discharges, reduced length of hospital stay, and improved outcomes[2]. However, the optimal timing of endoscopy in high-risk patients remains controversial. While some studies found no significant difference in mortality rates between urgent and early endoscopies, other studies reported a reduction in hospital stay and mortality after urgent endoscopies in patients with ANVUGIB[30,31]. The advancement of endoscopic therapy has brought down the hospitalization rate and mortality of UGIB over the last decade[32]. Therapeutic upper gastrointestinal endoscopy *via* EGD has been effective in achieving hemostasis[9,15]. Traditionally, endoscopic therapies achieving hemostasis have been classified into three categories: Injection therapy (involving injection of epinephrine, sclerosant, and thrombin), thermal therapy (with contact or non-contact probes causing electrocoagulation), and mechanical therapy (with clips, loops, and ligation)[15]. These modalities form the mainstay of standard endoscopic management. However, the advancement of newer endoscopic devices has the potential to improve outcomes in cases where conventional therapies fail to achieve hemostasis[15]. Several new hemostatic techniques have emerged over the past decade[15], which have been summarized in Table 3. These novel techniques have diverse approaches, ranging from upgrading current techniques to creating new technologies. Some of them have been incorporated into the current guidelines and are recommended as rescue or salvage therapies, while others should be considered when conventional interventions have failed[9]. For instance, hemostatic powders (non-absorbable mineral powders) can achieve immediate hemostasis by forming an adhesive mechanical barrier on contact with water and may be considered in ANVUGIB due to malignancy[9,20,27]. Current guidelines recommend over-the-scope clips (large-caliber clips that allow full circumferential tissue closure of large lesions) in select NVUGIB cases (especially cases of recurrent and persistent bleeding) where standard endoscopic modalities fail to stop the bleeding[9,20,27]. Over-the-scope clipping systems are fast gaining prominence as possible first-line endoscopic treat-

Table 1 Risk factors for non-variceal upper gastrointestinal bleeding

Risk factors	Value of parameter
History of peptic ulcer	
Helicobacter pylori infection	
Use of anticoagulant and antiplatelet drugs	
Prolonged INR	INR ≥ 1.21
Increase in leukocyte count	
Hypoalbuminemia	Serum albumin level < 35 g/L

INR: International normalized ratio.

Table 2 List of risk assessment scores for non-variceal upper gastrointestinal bleeding

Type of risk assessment score	Examples
Pre-endoscopy risk score	ABC score
	AIMS65 score
	CANUKA score
	Glasgow-Blatchford Score
	INBS
	MAP (ASH) score
	Pre-endoscopic Rockall score
Post-endoscopy risk score	Complete Rockall score
	CSMCPI score
	PNED score

ABC: Age, blood tests, co-morbidities; AIMS65: Albumin, International normalized ratio, Mental status, Systolic blood pressure, Age ≥ 65 years; CANUKA: Canada–United Kingdom-Adelaide; INBS: International bleeding score; MAP (ASH): Mental status, American Society of Anesthesiology classification, Pulse, Albumin, Systolic blood pressure, Hemoglobin; CSMCPI: Cedars Sinai Medical Centre Predictive Index; PNED: Progretto nazional emoragia digestive.

ments since they are shown to outperform standard endoscopic modalities in reducing the bleeding risk and mortality in high-risk cases of NVUGIB[15,20]. These advancements have the potential to plug the loopholes of conventional therapies, but they are not without their fair share of limitations[15,20]. Further large-scale studies are needed to identify their indications and validate their effects on morbidity and mortality before they can be fully incorporated into clinical practice.

CONCLUSION

ANVUGIB is a common medical emergency that has a high mortality rate despite its declining incidence. As the majority of patients are elderly, the increasing burden of comorbidities and the prevalence of risk factors in the geriatric population increase the likelihood of poor outcomes in high-risk groups. The increasing use of drugs such as NSAIDs, antiplatelet agents, and anticoagulants (especially in the elderly population) underscores the significance of obtaining a thorough drug history. Early risk stratification with validated scoring systems is the key to determining the line of management. Newly developed scores (like the ABC score and INBS), which are superior to the traditional scores in predicting outcomes, should be incorporated into clinical guidelines after obtaining good-quality evidence. Upper gastrointestinal endoscopies have both diagnostic and therapeutic applications and should be performed within 24 h of patient admission. Novel advancements in endoscopic therapies like hemostatic powder and over-the-scope clips have the potential to become first-line treatments in cases where standard endoscopic therapies are ineffective. Clinicians should be aware of the recent advances in risk stratification and endoscopic interventions in order to make informed decisions about targeted management for low- and high-risk patients. By integrating validated scoring systems and leveraging cutting-edge therapeutic modalities, clinicians can enhance patient care and mitigate the substantial morbidity and mortality associated with this critical condition.

Table 3 Summary of emerging endoscopic modalities for the management of non-variceal upper gastrointestinal bleeding

Modality type	Endoscopic modalities	Mechanism of action
Injection	Endoscopic ultrasound-guided angiotherapy	Controls variceal bleeding by deploying coils and injecting cyanoacrylate glue directly into targeted vessels, and confirming the thrombosis in real time with Doppler
Thermal	Coagulation grasper (Coagrasper)	A combination mechanical and thermal hemostasis device that delivers targeted monopolar coagulation at the precise site of bleeding
	Radiofrequency ablation	High-frequency alternating electrical current delivered to local tissue *via* radiofrequency electrode, causing thermal coagulative necrosis of the targeted tissue
	Cryotherapy	Induces cell necrosis through cycles of controlled local freezing and thawing of the tissue
	Endoscopic laser coagulation	Instantaneous hemostatic effect due to alterations in structural proteins in the vessel wall causing vessel shrinkage
Topical	Hemospray (TC-325 hemostatic powder)	Non-absorbable mineral powder that forms an adhesive mechanical barrier upon contact with water
	EndoClot (polysaccharide hemostatic powder)	Absorbable modified plant-based polymer that forms a protective gel matrix and concentrates coagulation factors upon contact with water
	Oxidized regenerated cellulose	Absorbable plant-based polymer that provides a matrix for clot formation and enhances platelet activation and adhesion
	Ankaferd Blood Stopper	Standardized mixture of plant extracts that induces formation of an encapsulated protein network which provides focal points for vital erythrocyte aggregation
Mechanical	Over-the-scope clip system	Large caliber clips made of metal alloy nitinol with shape-memory effect that stops bleeding by exerting constant circumferential compression force on the bleeding site
	Endoscopic suturing device	Excludes peptic ulcer from the intra-gastric acidic environment to prevent rebleeding
	Endoscopic band ligation	Complete obliteration of varices by causing mechanical strangulation with rubber bands

FOOTNOTES

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EDITORIAL

Navigating treatment resistance: Janus kinase inhibitors for ulcerative colitis

Jonathan Soldera

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Abstract

The management of refractory ulcerative colitis (UC) and acute severe UC (ASUC) is challenging due to the lack of standardized approaches in cases resistant to multiple treatments. In this editorial, I investigate the efficacy and safety of Janus kinase inhibitors, particularly upadacitinib and tofacitinib, in controlling severe and refractory disease. I highlight a notable case report by Xu *et al*, which explores the case of a patient with primary nonresponse to two classes of biologics and two fecal microbiota transplants who exhibited a remarkable response to upadacitinib. Furthermore, I discuss the use of tofacitinib in refractory UC and ASUC, either as monotherapy or in combination with biologics, which has shown promising response rates. Additionally, emerging evidence of upadacitinib efficacy in ASUC is presented. Overall, these cases emphasize the complex nature of managing refractory ASUC and the potential of small-molecule therapies to achieve remission. Further research is needed to refine treatment strategies for patients with treatment-resistant UC.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Janus kinase inhibitor; Upadacitinib; Tofacitinib; Infliximab

Core Tip: This editorial explores the efficacy and safety of Janus kinase inhibitors, specifically upadacitinib and tofacitinib, in refractory ulcerative colitis (UC) and acute severe UC (ASUC). Highlighting a compelling case report, it underscores the potential of these small-molecule therapies, either alone or in combination with biologics, to achieve and maintain disease remission. Furthermore, it emphasizes the importance of considering overlapping infections in ASUC and the need for prompt recognition by colorectal surgeons. This editorial advocates for further research to refine treatment strategies for patients with treatment-resistant UC, shedding light on promising therapeutic approaches.

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INTRODUCTION

Managing ulcerative colitis (UC), especially cases of refractory acute severe UC (ASUC), poses significant challenges due to poor patient response or intolerance to conventional and biological treatments. There is no standardized approach for cases resistant to multiple treatments. However, recent research has shed light on the efficacy and safety of small-molecule Janus kinase inhibitors, such as upadacitinib[1] and tofacitinib[2], in controlling severe and refractory disease.

JANUS KINASE INHIBITORS FOR REFRACTORY ULCERATIVE COLITIS

A report by Xu *et al*[3] describes the case of a patient who showed primary nonresponse to two biologics and two fecal microbiota transplants (FMT) but exhibited a remarkable response to upadacitinib[3]. It should be noted that FMT for ASUC is considered an off-label indication. The available evidence supporting its use remains primarily anecdotal, and its application should be restricted to the treatment of *Clostridioides difficile* (*C. difficile*) infection, or to clinical trials, according to the American Gastroenterology Association[4,5].

Despite limited evidence, both upadacitinib and tofacitinib have shown promise in the management of refractory UC, either as monotherapy or in combination with biologics as rescue therapy. At our center, we have extensive experience in employing off-label combined therapy for ASUC. I am particularly inclined to share a specific case that I believe would enrich the ongoing discussion initiated by Xu *et al*[3], presenting an alternative approach.

JANUS KINASE INHIBITORS AS RESCUE THERAPY FOR ULCERATIVE COLITIS REFRACTORY TO INFLIXIMAB

A 57-year-old male patient with a decade-long history of UC presented with recurrent symptomatic episodes despite several treatments. Initially responsive to mesalazine 4 g daily and a course of prednisone, the patient relapsed after a few years. Subsequent treatment with azathioprine 150 mg daily and mesalazine 4 g daily controlled the disease for another few years. However, his symptoms recurred, requiring the use of oral enteric budesonide 9 mg daily. Despite these interventions, his symptoms worsened, leading to fecal incontinence and anemia.

Tests for *C. difficile* toxins A and B and immunohistochemistry for cytomegalovirus were negative. Colonoscopy revealed worsening of UC (Figure 1), prompting initiation of biologic therapy with infliximab induction at a dose of 5 mg/kg. Although the patient reported a mild reduction in the frequency of bloody stools upon initiation of infliximab, fecal incontinence persisted. Despite dose escalation to 500 mg every 4 wk, his symptoms persisted, indicating a partial response to infliximab. Another colonoscopy was performed, which demonstrated improvement of mucosal damage, but without resolution of UC (Figure 2).

Tofacitinib 5 mg twice daily was introduced as adjunctive therapy alongside infliximab, replacing azathioprine, with the aim of achieving disease remission, as suggested in the case series by Gilmore *et al*[6]. Over the subsequent 3 months, the patient's symptoms gradually improved, with a reduction in stool frequency and resolution of fecal incontinence and bleeding. Treatment with tofacitinib was then interrupted, and the patient was maintained on infliximab 5 mg/kg/dose infusions every 6 wk, adjusted to infliximab serum levels, and azathioprine 100 mg daily. He has remained in deep remission for the last 3 years, with a Mayo endoscopic score of 0 (Figure 3).

There are two crucial points I believe warrant discussion. First, the possibility of overlapping infections in ASUC (*i.e.*, *C. difficile* and cytomegalovirus) was ruled out before escalation of therapy[7-9]. Second, colorectal surgeons must be aware that the clinical condition of patients with refractory UC or ASUC can rapidly deteriorate, requiring urgent colectomy[10,11].

There is increasing evidence supporting the utilization of tofacitinib in cases of infliximab-refractory ASUC[12]. A previous randomized controlled trial reported a response rate as high as 83% in ASUC patients refractory to corticosteroids after 7 d of tofacitinib treatment[13]. Similarly, a retrospective study demonstrated a response rate of 87.5%[14].

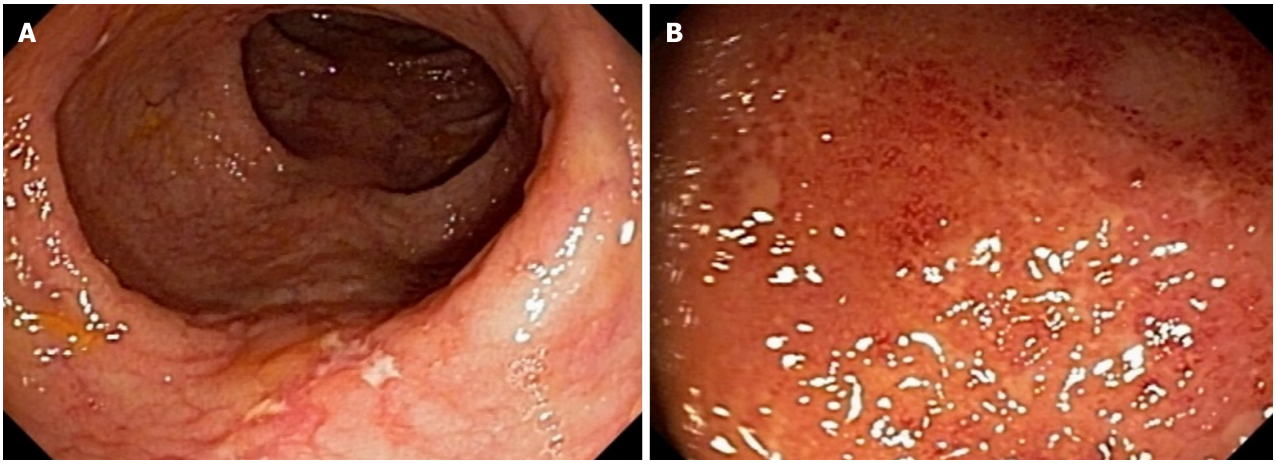

Figure 1 Colonoscopy. Pre-biologic. Ulcerative colitis with friability and ulcers, Mayo endoscopic score 2. A: Transition zone in the transverse colon; B: Sigmoid colon.

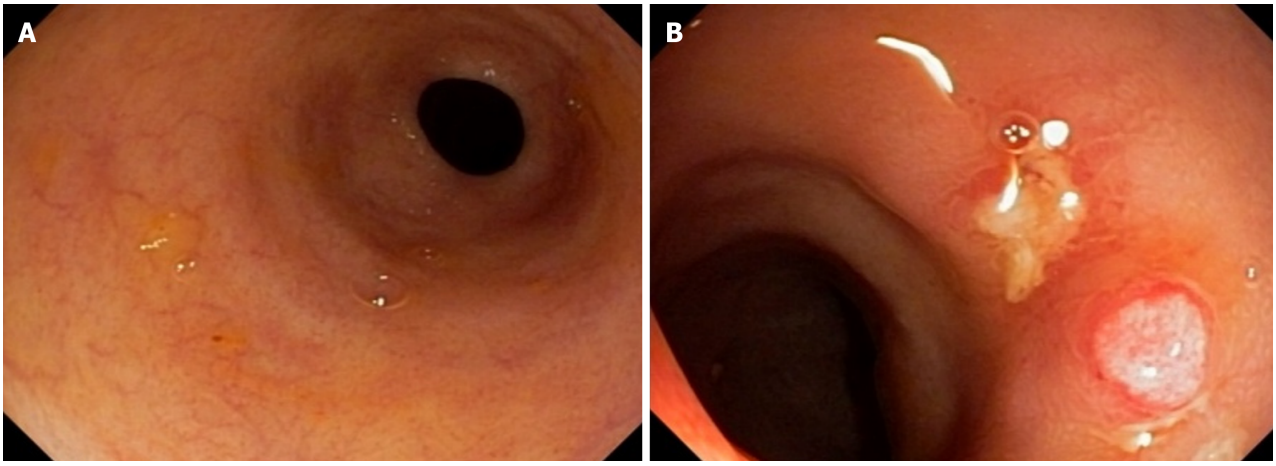

Figure 2 Colonoscopy. Pre-Tofacitinib. Improvement, but still presenting ulcerative colitis with patchy areas of friability and ulcers, Mayo endoscopic score 2. A: Transition zone in the transverse colon; B: Sigmoid colon.

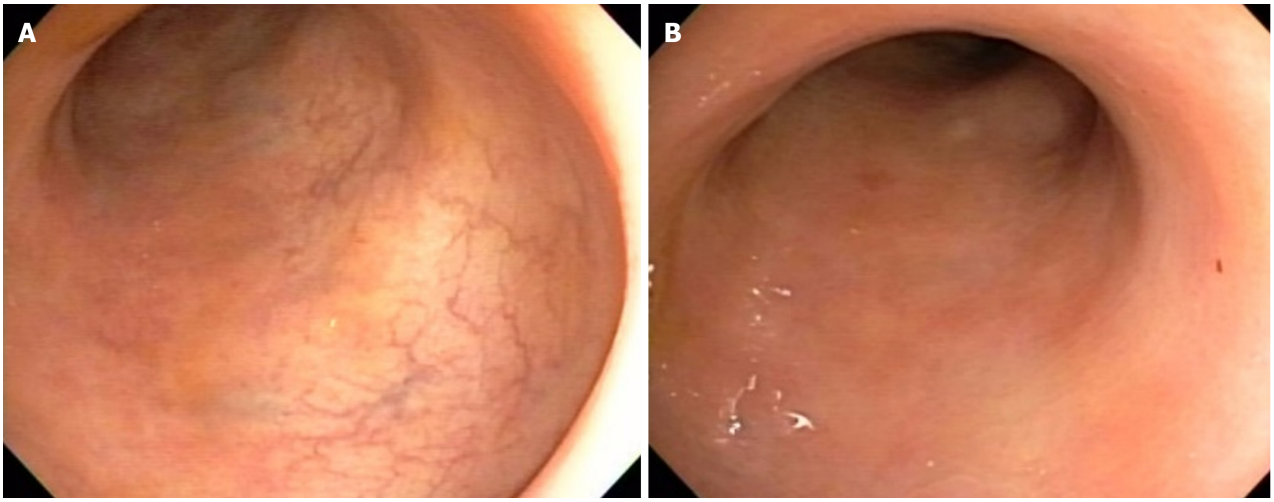

Figure 3 Colonoscopy. Maintenance therapy with infliximab, three years after tofacitinib was withdrawn. Scarred mucosa, Mayo endoscopic score 0. A: Transition zone in the transverse colon; B: Sigmoid colon.

Moreover, a noteworthy case series administered a higher dose of tofacitinib to eleven ASUC patients, achieving disease control in nine of them. Subsequently, these patients were transitioned to infliximab for maintenance therapy[15].

Tofacitinib has been investigated in combination with other biologics for the management of ASUC[16], including its use as replacement therapy for azathioprine alongside infliximab, demonstrating both efficacy and safety[6]. Of note, a systematic review revealed that the use of tofacitinib in ASUC led to a pooled 90-day and 6-month colectomy-free rate of 79.9%[17].

Although the use of tofacitinib as monotherapy in this setting has been extensively researched, some reports have also described the efficacy of upadacitinib in ASUC. For instance, a case report documented a positive response to upadacitinib in a patient for whom treatment with infliximab, adalimumab, and tofacitinib had previously failed[18]. A case series evaluating upadacitinib in ASUC resistant to steroids has demonstrated comparable efficacy to previous case series with tofacitinib, with 5 out of 6 patients showing improvement[19]. As upadacitinib has recently been approved for use in UC, promising results have been described in several recent case series of ASUC. One study reported steroid-free remission in 6 out of 9 patients[20], while another showed a response rate of 83% among 25 patients[21].

CONCLUSION

In conclusion, both cases underscore the complexity of managing refractory ASUC and highlight the potential synergistic effect of employing small molecule therapies either in combination or sequentially with biologics to achieve and sustain disease remission. Further studies are warranted to elucidate the optimal treatment strategies for patients who have completely or partially failed multiple available therapies.

FOOTNOTES

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EDITORIAL

Clues for diagnosing misplaced central venous catheter in the right ascending lumbar vein during right femoral venous access

Joho Tokumine, Kiyoshi Moriyama, Tomoko Yorozu

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Abstract

The right ascending lumbar vein is difficult to detect on anteroposterior abdominal radiographs because it overlaps with the inferior vena cava on anteroposterior radiographs. Intensive observation by medical providers may be a cue for diagnosis. However, knowledge of catheter misplacement of the right ascending lumbar vein is also necessary, because misplacement cannot be suspected without that awareness.

Key Words: Central venous catheter; Ascending lumbar vein; Femoral vein; Catheter misplacement; Anteroposterior abdominal X-ray

Core Tip: Intensive observation by medical providers is important to ensure early detection of a misplaced central venous catheter in the right ascending lumbar vein. However, knowledge of catheter misplacement of the right ascending lumbar vein is also necessary, because without that awareness, misplacement cannot be suspected.

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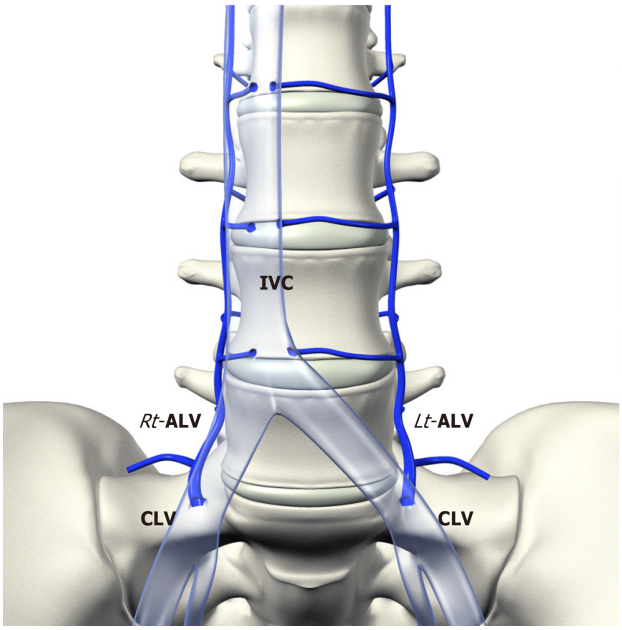

Figure 1 Anatomy of the ascending lumbar veins. IVC: Inferior vena cava; Rt-ALV: Right ascending lumbar vein; Lt-ALV: Left ascending lumbar vein; CIV: Common iliac vein.

INTRODUCTION

Zhu *et al*[1] reported a case in which a central venous catheter was mistakenly placed in the right ascending lumbar vein without symptoms or complications. Since the ascending lumbar vein is small, it can rupture and cause retroperitoneal hemorrhage if an irritant drug is administered through the misplaced catheter. Even without a rupture, catheter misplacement in the ascending lumbar vein may cause neurological symptoms because of its connection to the vertebral venous plexus[2]. Zhang *et al*[2] reported that complications caused by catheter misplacement in the ascending lumbar vein were observed in > 70% of the cases. Additionally, approximately 20% of the cases involved death due to complications[2].

ANATOMIC CONSIDERATIONS OF THE RIGHT ASCENDING LUMBAR VEIN

It is well-documented that a central venous catheter is misplaced in the left ascending lumbar vein during left femoral venous catheterization[2-7]. In contrast, it is extremely rare for a central venous catheter inserted through the right femoral vein to be misplaced in the right ascending lumbar vein[2,8-10]. The left common iliac vein runs curvature significantly before joining the inferior vena cava (Figure 1). Therefore, it is anatomically understandable that a catheter inserted from the left femoral vein would proceed to the left ascending lumbar vein, which is more in the straight direction. Conversely, a catheter inserted from the right femoral vein might be considered to pass through the confluence of the right ascending lumbar vein and the right common iliac vein.

WHAT'S THE CLUES FOR DIAGNOSING MISPLACEMENT?

The ascending lumbar vein runs along the lateral aspect of the vertebral body. Therefore, the left ascending lumbar vein is separated from the inferior vena cava and is more likely to be detected on an anteroposterior abdominal X-ray image[2-7]. In contrast, the right ascending lumbar vein is difficult to detect on anteroposterior abdominal radiographs because it overlaps with the inferior vena cava on anteroposterior radiographs[2,8-10]. Zhang *et al*[2] recommend the use of lateral abdominal X-ray images before computed tomography scan examination for efficacy and economy. However, in the absence of symptoms caused by catheter misplacement, there is no reason to suspect it, negating the need for ad-ditional lateral abdominal X-rays. Conversely, once symptoms appear, the patient's condition can rapidly deteriorate.

CONCLUSION

Intensive observation by medical providers is important in these cases. However, knowledge of catheter misplacement of the right ascending lumbar vein is also necessary, because without that awareness, misplacement cannot be suspected.

FOOTNOTES

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MINIREVIEWS

Exploration of the complex origins of primary constipation

Xing-Lin Zeng, Lian-Jun Zhu, Xiang-Dong Yang

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Abstract

Constipation is a common gastrointestinal disorder characterized by infrequent bowel movements and difficulty in passing stools. It can significantly affect an individual's quality of life and overall well-being. Understanding the causes of constipation is important for its effective management and treatment. In this paper, we have reviewed the primary causes of constipation or functional constipation. Primary constipation is a bowel disorder associated with colonic or anorectal sensorimotor or neuromuscular dysfunction. As per the literature, it is multifactorial and involves factors such as decreased interstitial cells of Cajal, altered colonic motility, enteric nervous system dysfunction, intestinal flora disturbances, and psychological influences. Clinical symptoms include difficulty in defecation, decreased frequency of defecation, or a feeling of incomplete evacuation. A comprehensive evaluation and management of constipation require an interdisciplinary approach incorporating dietary modifications, lifestyle changes, pharmacotherapy, and psychological interventions. Further research is imperative to explain the intricate mechanisms underlying constipation and develop targeted therapies for improved patient outcomes.

Key Words: Primary constipation; Pathogenesis factors; Treatment

Core Tip: The etiology of constipation is complex, involving a series of primary and secondary causes. Some of the primary factors reviewed in this paper include decreased interstitial cells of Cajal, altered colonic motility, enteric nervous system dysfunction, intestinal flora disturbances, and psychological influences. Clarifying the etiology of constipation can significantly facilitate the management of this disease through an interdisciplinary approach, incorporating dietary modifications, lifestyle changes, pharmacotherapy, and psychological interventions.

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INTRODUCTION

Constipation is a clinical condition with a high incidence rate. It is often difficult to manage and can induce cardiovascular and cerebrovascular diseases, as well as colorectal tumors[1,2]. Epidemiological studies suggest a global prevalence of constipation of 14%-26.8%[3,4], with the incidence continually increasing in parallel with the adoption of unhealthy lifestyle and dietary habits[5,6]. Based on the etiology, constipation can be categorized into primary and secondary types. Primary constipation, or functional constipation (FC), is a bowel disorder associated with colonic or anorectal sensorimotor or neuromuscular dysfunction[7-10]. The clinical symptoms of FC include difficulty in defecation, decreased frequency of defecation, or a feeling of incomplete evacua-tion. Importantly, the diagnosis of irritable bowel syndrome (IBS) with constipation must be excluded from FC, that is, neither abdominal pain nor abdominal distension should be the main presenting symptom. The clinical symptoms of constipation are generally present for at least 6 months before diagnosis and have occurred within the last 3 months. On the other hand, secondary constipation is linked with organic diseases (*e.g.*, colon stenosis or mass), medication use (*e.g.*, opioids and anticholinergics), or underlying conditions (*e.g.*, metabolic, thyroid, or diabetic disorders). Constipation can lead to the development of psychosomatic problems such as depression, anxiety, schizophrenia, and even suicidal tendencies. Furthermore, several patients with constipation experience sexual dysfunction, urinary retention, anal swelling, and other disorders, which significantly reduce their quality of life and affect their physical and mental health. To better understand constipation and device strategies to manage and cure the underlying causes of constipation, we have extensively reviewed relevant articles on the etiologies of primary constipation.

PRIMARY CONSTIPATION

The causes of primary constipation include factors such as interstitial cells of Cajal (ICCs), enteric nerves and neurotransmitters, intestinal flora, intestinal smooth muscle, age, sex, hormone levels, genetic factors, psychological and behavioral factors, and lifestyle factors (Figure 1; Table 1).

ICCs

ICCs are polymorphic cells located in the smooth muscles of the gastrointestinal tract. They play a crucial role in distributing and regulating the basic electrical activity of the gastrointestinal tract, mediating neural signals, and maintaining rhythmic motility. When ICCs mature to a fusiform or star shape, they develop 2-5 protrusions that form a network[11] whereby they establish tight junctions with the smooth muscles of the gastrointestinal tract through connexin 43[12]. Electron microscopy reveals synapse-like structures on the surface of ICCs that interact with gastrointestinal nerve endings to receive various neurotransmitters[13]. The ICC surface also features several ion channels related to K+, Ca^{2+}, and Cl-. Voltage-dependent Ca^{2+} channels are categorized into T-type and L-type channels. The T-type Ca^{2+} channels are closely associated with the generation of slow waves, while the L-type channels facilitate the entry of Ca^{2+} into the cell and its storage in the endoplasmic reticulum. Changes in the intracellular Ca^{2+} concentration trigger calcium oscillations, leading to the opening of the chloride channel (anoctamin 1, Ano1) in the plasma membrane, thus generating an inward current. Therefore, ICCs are crucial for regulating the slow-wave plateau phase and conduction[14]. ICCs contain small-conductance calcium-activated K+ channels, large-conductance K + channels, and ATP (triphosadenine) sensitive K+ channels. ATP-sensitive K+ channels regulate K+ inward flow and maintain the cell's resting potential at -70 mV. Changes in the ion channel expression may induce abnormal slow waves and disturbances in the gastrointestinal rhythm. When Ano1 is knocked out in mice, their intestinal rhythmicity, coordination, and contractility are significantly reduced [15]. The activation of K+ channels hyperpolarizes the cell membrane, causing gastrointestinal smooth muscle relaxation and inhibition of the pacing activity. Based on the layering of the intestinal wall, ICCs can be classified into submucosal ICCs, intermuscular ICCs, intramuscular ICCs, and deep muscular plexus ICCs[16]. Among these, intramuscular ICCs generate single potentials and are thus responsible for the relaxation of colonic smooth muscles, whereas intermuscular and submucosal ICCs generate slow waves to promote smooth muscle contraction[17]. Alterations have been noted in the number, morphology, and functions of colonic ICCs in constipation models[18]. The European guidelines state that

Table 1 The causes of constipation

Classification	Etiology	
Primary constipation	Intestinal flora	
	Interstitial cells of Cajal	
	Intestinal smooth muscle	
	Enteric nerves and neurotransmitters	
	Age and sex factors	
	Hormone levels	
	Hereditary factors	
	Psychological and behavioral factors	
	Lifestyles	
	Others	
Secondary constipation	Secondary conditions	Mechanical obstruction
		Metabolic disorders
		Neuropathy
		Anorectal disorders
		Others
	Medications	Anticholinergics
		Antipsychotics
		Analgesics
		5-HT receptor antagonists
		Others

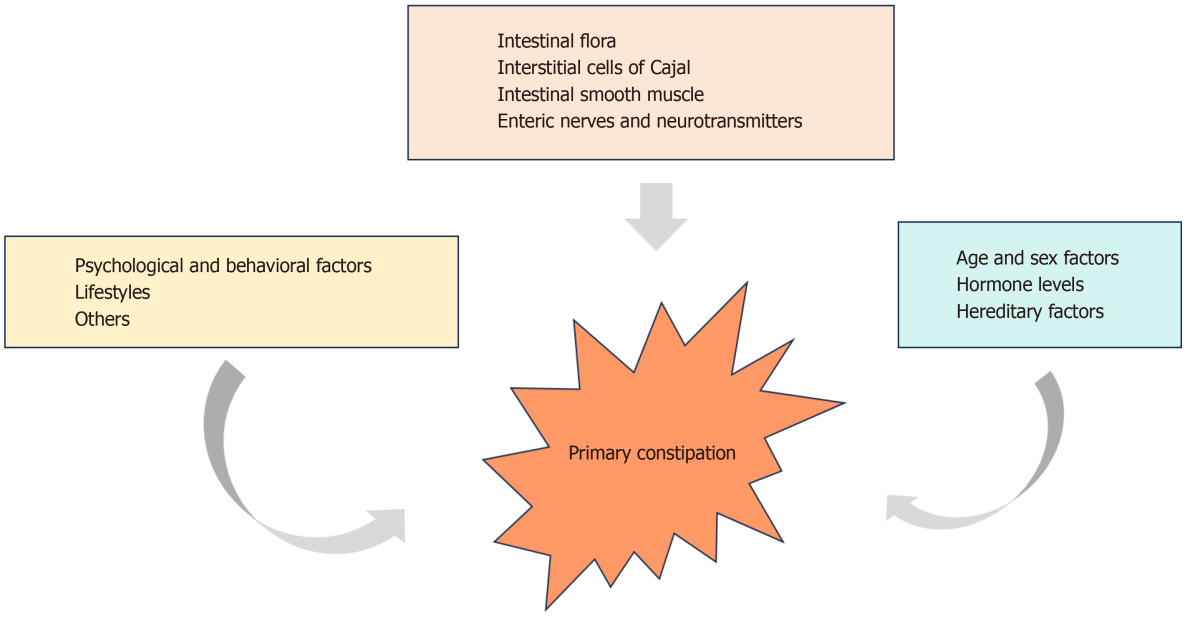

Figure 1 The causes of primary constipation.

colonic ICC volume is reduced in patients with constipation, which confirms the relationship between constipation with ICC[7].

Enteric nerves and neurotransmitters

Neuromodulation of the gastrointestinal tract is extraordinarily complex and is subject to regulation by the intrinsic

enteric nervous system, central nervous system, and visceral nervous system. ENS is a highly autonomous network composed of neurons, nerve fibers, and supporting cells within the digestive tract[19]. Numerous studies have confirmed abnormalities in the ENS of patients with slow-transit constipation (STC), including decreased neurons and glial cells, ultrastructural changes, and altered neurotransmitters. Furthermore, an enteric neuropathic disorder has been proposed as the essence of STC[20-23]. In the ENS, the excitatory neurotransmitters received by ICCs include neurokinin 1, NK3, acetylcholine, substance P, and 5-hydroxytryptamine, which promote the contraction of the intestinal wall and accelerate intestinal motility. Moreover, inhibitory neurotransmitters, such as nitric oxide, nitric oxide synthase, and vasoactive intestinal peptide, relax the intestinal wall[24-27].

Intestinal flora

Intestinal flora affects digestive tract development, participates in the formation of the immune system, and maintains digestive tract homeostasis. Attaluri *et al*'s findings have demonstrated that the prevalence of methanogenic flora was higher ($P < 0.05$) in the STC group (75%) than in the normal transit constipation (NTC) group (44%) or the control group (28%) ($P < 0.05$)[28]. The NTC group also produced more methane than the control group ($P < 0.05$), and the baseline, peak, and area under the curve of the methane response were moderately correlated with colonic transit ($P < 0.05$)[28]. Ohkusa *et al*[29] found that patients with IBS-C had reduced Actinobacteria counts in the fecal samples and increased Bacteroides levels in the mucosal samples when compared with healthy subjects. Moreover, treatment with synbiotics, probiotics, prebiotics, antibiotics, and fecal microbiota transplants improved the clinical symptoms in patients with constipation[29]. Gastrointestinal microorganisms, especially their populations, play a crucial role in maintaining the structural integrity of the gastrointestinal mucosal barrier, immune regulation, nutrient metabolism, and resistance to pathogens, mainly by increasing the expression of tight junction proteins (*i.e.*, ZO-1 and occludin), and their dysregulation is associated with FC and IBS-C[30].

Psychological and behavioral factors

The brain-gut axis is a bidirectional pathway linking cognitive and emotional centers to the neuroendocrine, ENS, and immune systems. On one hand, stimuli and intrinsic information connect to advanced nerve centers through the enteric nerve chain to affect gastrointestinal sensation, motility, and secretion. However, gastrointestinal functions can consecutively affect pain, emotions, and behavior in the central nervous system. Thus, psychophysiological abnormalities are the causal factors for gastrointestinal disorders. In Dykes *et al*'s study comprising 28 patients with constipation, 17 (61%) had a current psychiatric disorder and 18 (64%) had a history of psychiatric illness[31]. FC has also been associated with several behavioral factors. For example, Saps *et al*[32] studied 1334 children with functional gastrointestinal dis-orders and found that toilet-trained children were more likely to have FC than non-toilet-trained children.

Intestinal smooth muscles

Lesions of the intestinal smooth muscle can trigger altered colonic motility. Sun *et al*[33] found that the intestinal smooth muscle of STC rats was thinned, with intercellularly separated and disorganized atrophied cytosol. Zhong *et al*[34] found that drugs can improve constipation by promoting the assembly of actin filaments into tight bundles and stress fibers, thereby enhancing the contractility of intestinal smooth muscle cells. In addition, many studies[35,36] have pointed out that the occurrence of constipation is related to the significant thinning of intestinal smooth muscle and the decrease of intestinal contractility.

Age and sex factors

According to an epidemiological investigation, the ratio of female to male patients with constipation was 2.2:1, with the chances of constipation increasing with age, as has been evidenced in individuals aged > 65 years due to decreased intestinal peristaltic function[37]. Another study reported an overall prevalence of FC of 26.8%, which was significantly higher in women than in men ($P = 0.019$)[4]; this difference may be attributed to the fact that women are at a higher risk of injury to the pelvic floor muscles and nerves required for defecation[4].

Hereditary factors

Chan *et al*'s survey of first-degree relatives and spouses of adult patients with chronic constipation meeting the Rome II criteria revealed that the prevalence of constipation among relatives of patients with constipation was 16.4%[38], whereas that among the relatives of patients without constipation was 9.1%, suggesting that family members of patients with constipation are at a higher risk of developing constipation.

Lifestyles

It is widely accepted that diet is closely associated with constipation[39,40]. For instance, in Jung *et al*'s study[41], for patients with FC, brown rice-based and wheat-based diets led to improved bowel functions as a result of reduced bowel transit time and increased bowel movements when compared with white rice-based diets. Furthermore, appropriate exercise has been suggested to relieve constipation symptoms[42], although some scholars disagree[43]. Owing to the methodological shortcomings, the actual effect of exercise on constipation cannot be definitively determined, warranting further prospective studies in this direction.

Hormone levels

Ulusoy *et al*[44] compared 91 children with constipation and 100 healthy controls and found that the serum gastric motility levels were significantly lower in children with constipation than in healthy controls ($P = 0.008$), suggesting re-

duced serum gastric motility levels in children with constipation. Cong *et al*'s findings suggest that an impaired STC motor index is the result of abnormal cyclooxygenase and prostaglandin levels[45], possibly due to the overexpression of progesterone receptors resulting in myocytes becoming more sensitive to the circulating progesterone levels. For instance, estrogens have been reported to impair the contraction of colonic smooth muscles, leading to constipation in mice[46,47]. However, evidence regarding the role of estrogens in human constipation is lacking.

TREATMENT

First-line therapies for the treatment of constipation comprise discussing the appropriate and customized diet, exercise, and bowel-management techniques relevant to the patient's case. Current recommendations suggest that women should consume 20-28 g of fiber and men should consume 30-38 g of fiber in their diets daily, and physical activity should be encouraged in able-bodied patients[48]. Other measures, such as establishing a regular defecation routine and proper toileting habits, are also recommended[49]. If first-line therapies are unsuccessful, pharmacological therapies, such as the use of calcium polycarbophil, psyllium, polyethylene glycol, bisacodyl, and others, should be considered as the next therapeutic option. However, these medications are associated with side effects and may not be always effective[50]. Novel approaches combining several measures need to be explored in larger clinical trials to strategize ways to better manage the disease.

CONCLUSION

Constipation significantly affects the physical and mental health of individuals. The etiology of constipation is complex, involving a series of primary and secondary causes. Some of the primary factors reviewed in this paper include decreased ICC, altered colonic motility, ENS dysfunction, intestinal flora disturbances, and psychological influences. Clarifying the etiology of constipation can significantly facilitate the management of this disease through an interdisciplinary approach, incorporating dietary modifications, lifestyle changes, pharmacotherapy, and psychological interventions.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Influence of humanistic care-based operating room nursing on safety, recovery, and satisfaction after radical surgery for colorectal carcinoma

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Abstract

BACKGROUND

Radical surgery is a preferred treatment for colorectal carcinoma, wherein nursing intervention is essential for postoperative recovery and prevention of complications. Recently, the application of humanistic care in medical care has attracted attention. Humanistic care emphasizes comprehensive care, with importance attached to patients' physical needs as well as psychological and emotional support to provide more humane and personalized care services. However, no clinical reports have examined the use of humanistic care in patients undergoing radical surgery for colorectal carcinoma.

AIM

To investigate the influence of humanistic care-based operating room nursing on the safety, postoperative recovery, and nursing satisfaction of patients who have undergone radical surgery for colorectal carcinoma.

METHODS

In total, 120 patients with rectal cancer who underwent surgery in Zhongnan Hospital of Wuhan University between August 2023 and March 2024 were selected and grouped based on the nursing methods employed. Of these patients, 55 were treated with routine nursing intervention (control group) and 65 were provided humanistic care-based operating room nursing (research group). The patients' vital signs were recorded, including systolic/diastolic blood pressure (SBP/DBP) and heart beats per minute (BPM), as well as serum stress indices, including norepinephrine (NE), adrenal hormone (AD), and cortisol (Cor). Postoperative recovery and complications were also recorded. Patients' negative emotions, life hope, and nursing satisfaction were evaluated using the Self-rating Depression/Anxiety Scale (SDS/SAS), Herth Hope Index (HHI), and self-deve-

loped nursing satisfaction questionnaire, respectively.

RESULTS

During emergence from anesthesia, SBP, DBP, and BPM levels were found to be lower in the research group than those in the control group, also serum Cor, AD, and NE levels were lower. In addition, the research group had shorter operative, awakening, anal exhaust, first postoperative ambulation, drainage tube removal, intestinal recovery, and hospital times. The total complication rate and the SDS and SAS scores were lower in the research group than those in the control group. The HHI and nursing satisfaction scores were higher in the research group.

CONCLUSION

Humanistic care-based operating room nursing can mitigate physiological stress responses, reduce postoperative complications, promote postoperative recovery, relieve adverse psychological emotions, and enhance life hope and nursing satisfaction in patients undergoing radical surgery for colorectal carcinoma, which can be popularized in clinical practice.

Key Words: Humanistic care; Nursing; Radical surgery for rectal carcinoma; Stress response

Core Tip: Currently, no clinical studies have reported the application of humanistic care-based operating room nursing in patients who underwent radical surgery for colorectal carcinoma. This study explored the impact of humanistic care-based operating room nursing on the physiological stress, postoperative recovery, and nursing satisfaction of such patients. The results revealed that humanistic care-based operating room nursing can significantly relieve patients' physiological stress responses, reduce postoperative complications, promote postoperative recovery, alleviate negative psychological emotions, and increase life hope and nursing satisfaction. This indicated promising clinical promotion value of this nursing model.

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INTRODUCTION

Colorectal carcinoma (CRC) is one of the most common gastrointestinal malignancies, with nearly 1.8 million new cases and 881000 related deaths worldwide, accounting for approximately 10% of cancer-related deaths[1]. As a CRC subtype, rectal cancer accounts for one-third of newly diagnosed CRC cases annually[2]. The etiology of rectal cancer is currently unknown; however, it may be related to environmental factors, eating habits, and genetic factors[3]. Currently, surgical treatment remains the first choice for rectal cancer treatment. However, because of varying degrees of pain, vomiting, dizziness, anxiety, depression, and fear perioperatively, patients' ability to cope with cancer and compliance with treatment are reduced, which seriously affects the recovery process and quality of life[4]. Therefore, it is important to provide scientific and reasonable nursing care during the perioperative period, which is a necessary to improve surgical safety.

Traditional nursing is mainly disease-centered, lacking planning, pertinence, and enthusiasm, resulting in difficulty in meeting people's increasingly demanding nursing needs. In this context, several new patient-centered nursing models have emerged and have achieved better nursing quality than traditional nursing in various nursing settings, demonstrating several clinical application prospects[5]. Being patient-centered, the humanistic care theory emphasizes that nursing care for patients is a reflection of interpersonal activities, human nature, and emotions in the nursing process, thereby making the nursing process more humanistic and improving patient comfort[6,7]. Patients with cancer are at risk of serious psychological burden and negative emotions, including despair, depression, and anxiety because of factors such as a decline in physical function, increased economic pressure, and self-cognitive disorders, which seriously affect their physical and mental health[8]. Therefore, patients with cancer require more humane care services during treatment. The humanistic care-based nursing model has been shown to significantly improve the rehabilitation of patients after ovarian cancer surgery, reduce physical and mental stress responses, and effectively enhance nursing satisfaction and quality of life[9]. In addition, in patients receiving chemotherapy for malignancies, self-efficacy intervention combined with humanistic nursing significantly improved their self-care ability, quality of life, and nursing satisfaction[10]. These studies have suggested that humanistic care-based nursing can effectively meet the nursing quality needs of patients with cancer. However, no clinical studies have reported humanistic care-based operating room nursing for patients undergoing radical surgery for rectal carcinoma.

In this study, 120 patients who underwent surgery for rectal cancer at our hospital were collected and grouped into receiving routine operating room nursing or humanistic care-based nursing. The application value of humanistic care-based operating room nursing in rectal cancer surgery was evaluated by comparing physiological stress, postoperative

recovery, emotions, and complications between the two groups.

MATERIALS AND METHODS

Study participants

A total of 120 patients with rectal cancer who underwent surgery at Zhongnan Hospital of Wuhan University between January 2023 and January 2024 were included in the study. They were grouped based on differences in nursing modalities. The control group included 55 patients treated with routine nursing, whereas the research group included and 65 patients who were given humanistic care-based operating room nursing.

Treatment-naive patients (aged 18–70 years) who were diagnosed with rectal cancer by digital rectal examination, pathological findings, and imaging, with tumor–node–metastasis (TNM) stage of T1–T2, America Society of Anesthesiologist (ASA) grades I–II, complete clinical data, without heart, kidney, and liver dysfunction, other malignancies, history or family history of mental illness, or special medication history were included. Patients with serious heart, liver, kidney, or other vital organ function diseases; coagulation, endocrine, and immune dysfunctions; mental disorders; complicated conditions such as burns, poisoning, and unique pathogenic infections; or referrals were excluded.

Nursing

The control group received routine care, which included basic nursing services as instructed by the doctor, vital sign monitoring, infusion care, medication care, scheduled patrols, and dietary guidance.

The research group received humanistic care-based operating room nursing, as specified below:

Strengthening preoperative inspection: The medical staff assessed patients' vital signs, understood their past medical history, understood the specific conditions, and developed individualized nursing plans according to the actual patient situation. To enhance patients' rehabilitation beliefs and compliance behaviors and improve their cooperation with treatment and nursing, nurses strengthened patients' and their families' understanding regarding treatment advantages, nursing significance, and rehabilitation exercises by playing videos, providing oral explanations, and distributing publicity brochures. Furthermore, to improve the self-restraint ability and correct bad habits and behaviors of the patients, the medical staff educated the patients about the positive effects of a reasonable diet, good life work, and rest on disease rehabilitation, providing favorable conditions for their rehabilitation. Patients were also cared for psychologically by identifying their negative emotions, such as nervousness, anxiety, and depression, analyzing factors that cause psychological burden according to the actual situation, and guiding them to use music, meditation, breathing, and talking to divert their attention and eliminate tension, anxiety, and other negative emotions. Moreover, nurses enhanced patients' confidence in surgical treatment by introducing successful cases.

Strengthening preoperative preparation: The operating bed was preheated 30 min before surgery, and the temperature and humidity in the operating room were adjusted reasonably. To eliminate the patient's nervousness about the unfamiliar environment, nurses warmly received the patient at the door of the operating room and explained the operating room environment and personnel composition. Simultaneously, nurses encouraged and comforted patients through communication, lifted their enthusiasm for treatment, reduced negative emotions, and strengthened their confidence in surgery. Furthermore, the operating room was kept quiet and tidy, and devices were moved as gently as possible to avoid noise stimulation.

Enhancing intraoperative care: To reduce patients' fear of medical procedures, nurses explained the purpose of each procedure before the administration of anesthesia. During anesthesia, nurses gently held the patient's hands or shoulders, gave him/her spiritual comfort, and distracted his/her attention *via* conversation to ensure smooth completion of the process. Regarding body positioning, nurses moved the patient gently to ensure patient comfort. Intraoperatively, pressure sores were prevented by cotton pads, and insulation measures were taken by covering patients with heated blankets, reducing unnecessary exposure, and heating the infusion liquid. Aseptic operation was performed in strict accordance with the specific operating room requirements during the procedure. Nurses also closely monitored the changes in patients' vital signs and reported them to doctors on time during emergencies such as dyspnea or increased heart rate. During surgery, the nursing staff closely cooperated with the physicians to execute surgery-related care, such as assisting the physicians in providing the operation-related equipment and removing related obstacles affecting the surgical process.

Strengthening postoperative care: Postoperatively, nurses adjusted the patient to a comfortable position, encouraged him/her to exercise according to the recovery status, and massaged his/her limbs regularly to prevent lower limb venous thrombosis. Strict postoperative nursing care of the indwelling catheter was also performed. Vital signs of the patients were monitored in real time to avoid risk factors leading to incisional infection. Patients were allowed to eat liquid food rather than solid when intestinal peristalsis was not restored, and small and frequent meals were advocated after recovery of intestinal peristalsis.

Outcome measures

Vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart beats per minute (BPM), were recorded. Venous blood was collected before and during emergence from anesthesia and centrifuged to collect serum for the measurement of norepinephrine (NE), adrenal hormone (AD), and cortisol (Cor) levels.

The operative, awakening, anal exhaust, first postoperative ambulation, drainage tube removal, intestinal function recovery, and hospitalization times were recorded. The occurrence of common complications such as infection, agitation, anastomotic fistula, nausea and vomiting, and ileus were also recorded.

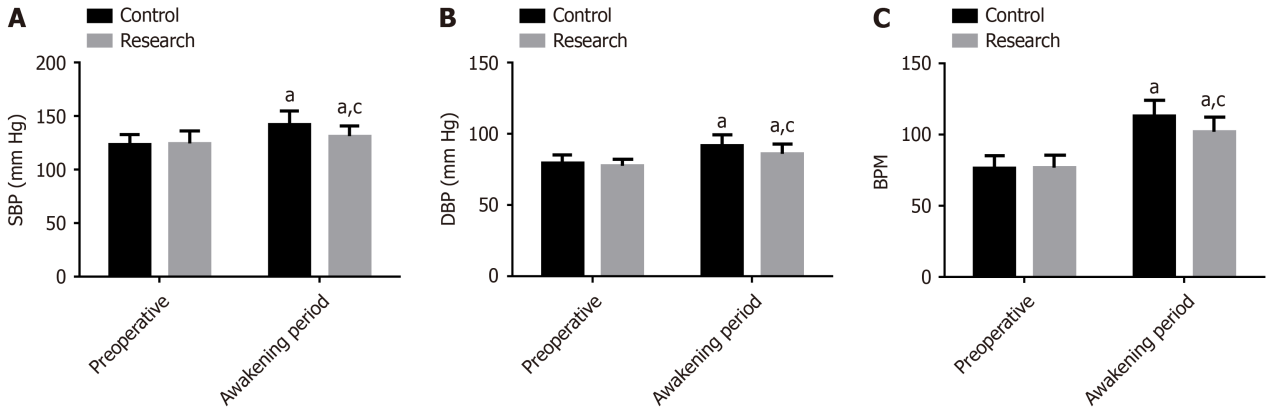

Figure 1 Comparison of vital signs at different surgical stages. A: Systolic blood pressure levels; B: Diastolic blood pressure levels; C: Heart beats per minute levels. $^{a}P < 0.05$ within the group before and after treatment. $^{c}P < 0.05$ compared with the control group at the same surgical stage. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BPM: Heart beats per minute.

Changes in negative emotions before and after nursing interventions were assessed using the Self-rating Depression/Anxiety Scale (SDS/SAS). The SDS consists of 20 items using a 4-point scale. Higher SDS and SAS scores indicate severe depression and anxiety.

The Herth Hope Index (HHI) was used in life hope assessment of patients. The scale is divided into three dimensions: Temporality and future, positive readiness and expectancy, and interconnectedness, each with four items scored on a 4-point scale. With a total score ranging 12–48, a higher score indicated a higher degree of hope. Scores of 12–23, 24–35, and 36–48 points indicate a low, moderate, and high level of hope, respectively.

Nursing satisfaction surveys were used to assess patients' satisfaction with nursing tasks, which were divided into three levels: Satisfied (high recognition and affirmation), basically satisfied (recognition and affirmation), and dissatisfied (disapproval)[11]. Satisfaction = (very satisfied cases + basically satisfied cases)/total number of cases × 100%.

Statistical analysis

Statistical analysis and image rendering of data was conducted using SPSS 21.0 and GraphPad Prism 6, respectively. Chi-square or Fisher's exact test was used to compare the counting data. The Kolmogorov-Smirnov test was used to analyze the distribution of continuous data, in which normally distributed data were described as the mean ± SD. Independent samples *t*-test (two-tailed) was used for intergroup comparisons of measurement data and paired *t*-test (two-tailed) for intragroup comparisons between different periods, with $P < 0.05$ representing statistical significance.

RESULTS

Comparison of the general data

No significant differences were found in terms of sex, age, eating habits, working status, education level, ASA grade, TNM stage, pathological type, and other general clinical data between the two groups ($P > 0.05$) (Table 1).

Comparison of vital signs

Preoperative SBP, DBP, and BPM were comparable between the groups ($P > 0.05$). Postoperative SBP, DBP, and BPM significantly increased in both groups, with levels lower in the research group than in the control group ($P < 0.05$) (Figure 1).

Comparison of the physiological stress response indices

No significant intergroup differences were found in the preoperative levels of Cor, AD, and NE ($P > 0.05$). Compared with the preoperative values, preoperative Cor, AD, and NE levels increased markedly in both groups, with lower levels in the research group than that in the control group ($P < 0.05$) (Figure 2).

Comparison of the intraoperative and postoperative indices

Compared with the control group, research group had shorter operative, awakening, anal exhaust, first postoperative ambulation, drainage tube removal, intestinal function recovery, and hospitalization times ($P < 0.05$) (Table 2).

Comparison of postoperative complications

Postoperative complications were recorded in both groups. In the control group, 2 cases of infection, 4 of agitation, 1 of anastomotic fistula, 6 of nausea and vomiting, and 2 of ileus were recorded, with a total incidence of 27.27%. In the research group, only 1 case of infection, 4 of nausea and vomiting, and 1 of ileus were noted, with an overall incidence of 9.23%. The research group had a lower total complication rate than that of the control group ($P < 0.05$) (Table 3).

Table 1 Comparison of general data [*n* (%), mean ± SD]

Groups	Control group (*n* = 55)	Research group (*n* = 65)	χ^2/t	*P* value
Age (years)	51.23 ± 11.28	54.55 ± 10.77	1.646	0.102
Sex			0.616	0.432
Female	19 (34.55)	27 (41.54)		
Male	36 (65.45)	38 (58.46)		
Eating habits			0.677	0.411
Light	14 (25.45)	21 (32.31)		
Greasy	41 (74.55)	44 (67.69)		
Working status			0.271	0.603
Employed	22 (40.00)	23 (35.38)		
Unemployed	33 (60.00)	42 (64.62)		
Educational level			0.808	0.369
≥ high school	23 (41.82)	22 (33.85)		
< high school	32 (58.18)	43 (66.15)		
ASA grade			0.103	0.748
I	27 (49.09)	30 (46.15)		
II	28 (50.91)	35 (53.85)		
TNM stage			0.073	0.788
T1	19 (34.55)	24 (36.92)		
T2	36 (65.45)	41 (63.08)		
Pathological type			0.809	0.667
Papillary adenocarcinoma	29 (52.73)	37 (56.92)		
Tubular adenocarcinoma	16 (29.09)	20 (30.77)		
Mucinous adenocarcinoma	10 (18.18)	8 (12.31)		

TNM: Tumor–node–metastasis.

Table 2 Comparison of perioperative indicators (mean ± SD)

Groups	Control group (*n* = 55)	Research group (*n* = 65)	χ^2	*P* value
Operation time (min)	54.91 ± 9.08	47.95 ± 7.23	4.673	< 0.001
Awakening time (h)	34.05 ± 6.30	27.26 ± 4.68	6.762	< 0.001
Anal exhaust time (h)	19.16 ± 4.16	15.28 ± 3.77	5.357	< 0.001
First postoperative ambulation time (h)	8.42 ± 2.64	7.14 ± 2.28	2.850	0.005
Drainage tube removal time (h)	6.16 ± 1.41	5.35 ± 1.87	2.639	0.009
Intestinal function recovery time (h)	28.22 ± 5.56	22.85 ± 5.65	5.226	< 0.001
Hospitalization time (d)	8.73 ± 2.74	7.57 ± 2.38	2.482	0.015

Comparison of emotional ratings

The preoperative SDS and SAS scores were comparable between the groups ($P > 0.05$). Compared with preoperative scores, the scores on both scales reduced statistically after surgery, particularly in the research group ($P < 0.05$) (Figure 3).

Comparison of life hope scores

The two groups showed no notable differences in the scores of various dimensions of the HHI scale and the total score ($P > 0.05$). Both groups had high HHI scores after surgery, in terms of each dimension or the overall scale, with even more

Table 3 Comparison of postoperative complications, *n* (%)

Groups	Control group (*n* = 55)	Research group (*n* = 65)	*t*	*P* value
Infection	2 (3.64)	1 (1.54)	-	-
Agitation	4 (7.27)	0	-	-
Anastomotic fistula	1 (1.82)	0	-	-
Nausea and vomiting	6 (10.91)	4 (6.15)	-	-
Ileus	2 (3.64)	1 (1.54)	-	-
Total incidence	15 (27.27)	6 (9.23)	6.717	0.010

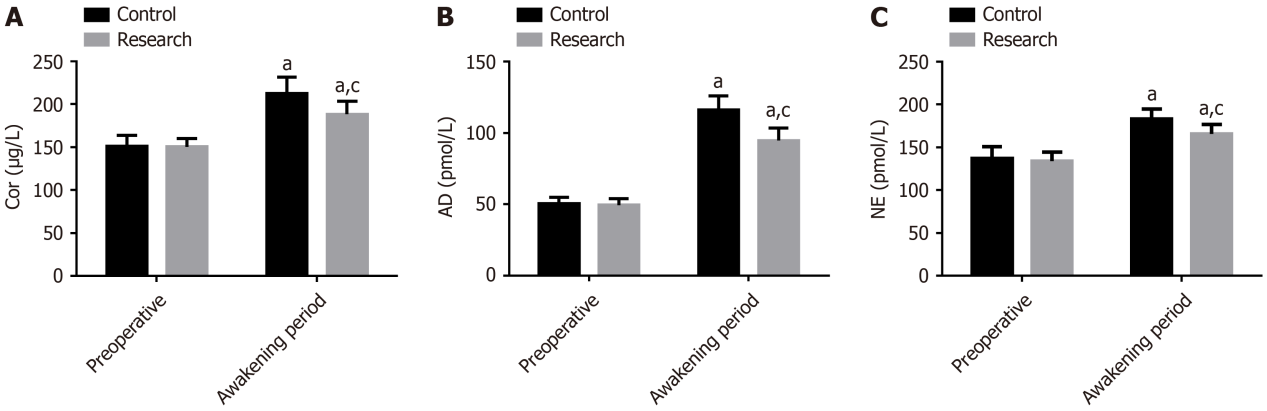

Figure 2 Comparison of physiological stress response indices at different surgical stages. A: Cortisol levels; B: Adrenal hormone levels; C: Norepinephrine levels. [a]*P* < 0.05 within the group before and after treatment. [c]*P* < 0.05 compared with the control group at the same surgical stage. AD: Adrenal hormone; Cor: Cortisol; NE: Norepinephrine.

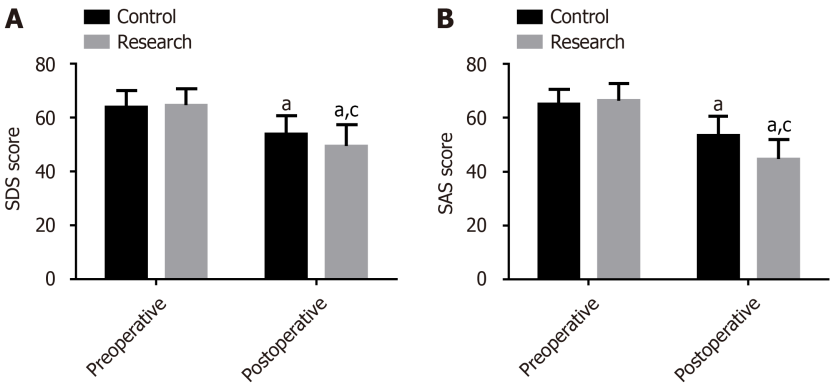

Figure 3 Comparison of emotional scores. A: Comparison of Self-rating Depression Scale scores at different surgical stages; B: Comparison of Self-rating Anxiety Scale scores at different surgical stages. [a]*P* < 0.05 within the group before and after treatment. [c]*P* < 0.05 compared with the control group at the same surgical stage. SDS: Self-rating Depression Scale; SAS: Self-rating Anxiety Scale.

noticeable increases in the research group ($P < 0.05$) (Figure 4).

Comparison of nursing satisfaction scores

In the analysis of patient nursing satisfaction, the satisfaction rate (76.36%) of the control group was significantly lower (95.38%) than that of the research group ($P < 0.05$) (Table 4).

DISCUSSION

Compared with other surgeries, tumor resection is characterized by great trauma, complex procedure, and long duration; hence, increased assistance of nurses is required. Most current nursing tasks in the operating room involve functional

Table 4 Comparison of nursing satisfaction scores, *n* (%)

Groups	Control group (*n* = 55)	Research group (*n* = 65)	χ^2	*P* value
Satisfied	12 (21.82)	30 (46.15)	-	-
Basically satisfied	30 (54.55)	32 (49.23)	-	-
Dissatisfied	13 (23.64)	3 (4.62)	-	-
Overall satisfaction	42 (76.36)	62 (95.38)	9.328	0.002

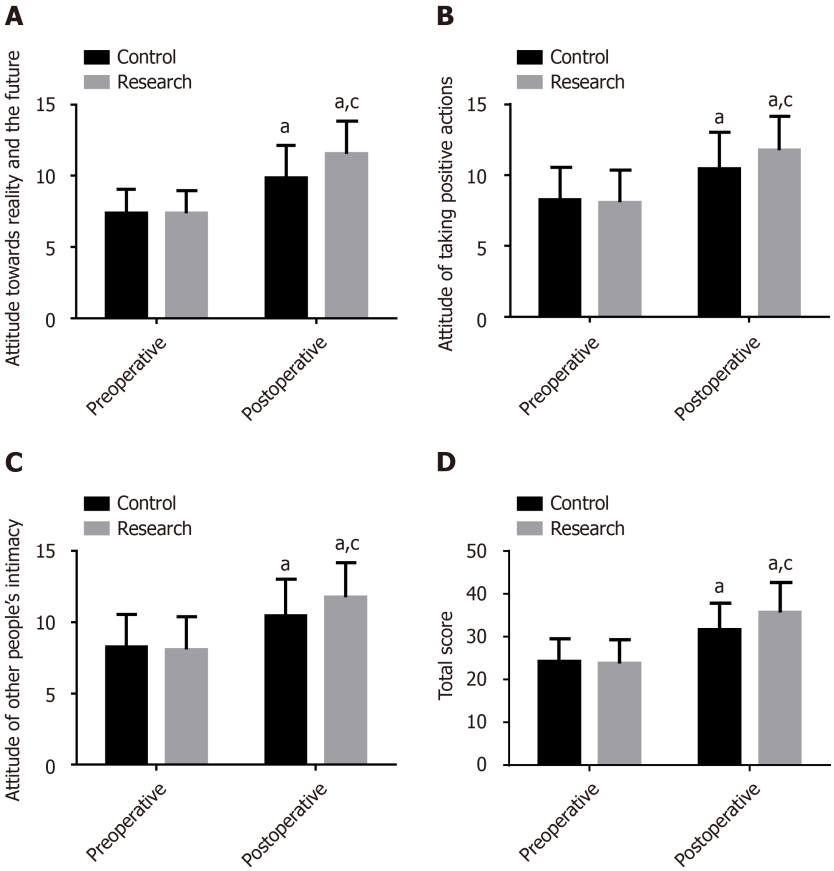

Figure 4 Comparison of life hope scores at different surgical stages. A: Temporality and future scores; B: Positive readiness and expectancy scores; C: Interconnectedness scores. D: Total Herth Hope Index scores. $^{a}P < 0.05$ within the group before and after treatment. $^{c}P < 0.05$ compared with the control group at the same surgical stage.

nursing, focusing on simply caring for diseases, which makes it difficult to meet the diverse needs of patients[12]. Humanistic care refers to the ability, attitude, and behavior in patient-centered care provided by caregivers, which helps patients achieve physical, spiritual, and sociocultural well-being and gain a sense of security by making them feel cared for and respected in the care process[13]. Although humanistic care has been proposed for decades, nurses pay more attention to nursing skills than humanistic care, with some only focusing on disease treatment and neglecting patient interaction[14]. Past clinical experience has shown that the awareness and ability of medical staff to provide humanistic care are key factors affecting patients' psychological state, treatment outcomes, and overall rehabilitation[15].

Rectal cancer is a major digestive disorder, and the inevitable mechanical stimulation during abdominal surgery, severe pain at the end of anesthesia, and adverse emotions can excite the sympathetic nervous system, triggering stress reactions, hindering gastrointestinal peristalsis, and making it impossible for patients to exhaust and defecate normally [16-18]. If the condition worsens, flatulence, intestinal adhesion, abdominal wall adhesion, and even intestinal infarction may occur, thereby endangering the patient's life. Previous studies have shown that reducing the perioperative stress response of patients undergoing radical surgery for CRC is conducive to gastrointestinal function recovery[19]. Intraoperative hypothermia may cause sympathetic nerve excitement, resulting in intraoperative hemodynamic fluctuations. In addition, hypothermia is associated with various adverse effects, such as increased infection risk, prolonged hospitalization, high healthcare costs, and coagulopathy[20]. Therefore, individualized psychological care can effectively alleviate patients' negative psychological emotions, enhance their confidence in facing diseases, and reduce their psychological stress responses[21]. Considering that patients may have poor surgical outcomes because of physiological or psychological stress, they require psychological support and intraoperative thermal insulation measures.

The results of this study showed that compared with the patients of the control group, patients of research group had more stable vital signs during emergence from anesthesia, better serum stress response levels, shorter operative and postoperative recovery times, greater relief of negative emotions, and lower overall complication rates.

Rectal cancer is a life-threatening condition that predisposes patients to severe psychological stress and significant changes in lifestyle and habits postoperatively. Patients are susceptible to negative emotions such as depression and anxiety[22], adversely affecting their physiology, immunity, and social activities if not tended to properly[23]. Meanwhile, they may lose confidence and may not actively cooperate with doctors' treatment, which affects treatment compliance and quality of life[24]. Therefore, increasing patients' hope for life is an important part of nursing. In this study, the postoperative scores of various HHI dimensions and the total HHI score were higher in the research group than in the control group, because of the following reasons: First, we formulated a highly personalized nursing model according to patients' different educational levels, family status, income status, and psychological endurance, which can relieve patients' psychological pressure and improve their treatment compliance. Second, personalized health education was provided to patients, enabling them to have some understanding of the disease and its corresponding treatment plans and reducing negative emotions caused by unknown factors. Third, encouragement and support from nursing staff and family members can enhance patients' confidence in facing the disease, thus improving their life hope. Finally, the satisfaction of the control group was 76.36%, which was significantly lower than that of the research group. Therefore, it can be stated that the traditional nursing model can no longer meet the needs of patients, and humanistic care-based operating room nursing has high application value in radical surgery for rectal cancer.

This study has some limitations that must be addressed. First, the sample size was small, which led to statistical calculations when comparing some results. Second, each operating room did not have the same nursing team; the professional ability of nurses may be different, which may affect the quality of care to varying degrees. Third, the long-term postoperative recovery of the patients was not assessed because of the short research period. Hence, in-depth and comprehensive experimental analyses in the future are required to address these limitations.

CONCLUSION

In summary, humanistic care-based operating room nursing has high application value in radical surgery for rectal cancer, which can mitigate negative emotions, facilitate postoperative recovery, reduce postoperative complications, and improve the life hope and nursing satisfaction of patients, with high clinical promotion value.

FOOTNOTES

Author contributions: Wang XP designed the research study; Wang XP and Niu M performed the research; Wang XP and Niu M analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethic Committee of Zhongnan Hospital of Wuhan University.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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

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ORIGINAL ARTICLE

Retrospective Study

Correlation between TEX14 and ADAM17 expressions in colorectal cancer tissues of elderly patients and neoplasm staging, invasion, and metastasis

Gun Chen, Ling-Hua Cong, Chi-Jiang Gu, Ping Li

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Abstract

BACKGROUND

Colorectal cancer (CRC) is one of the most frequently encountered malignant tumors in clinical settings. Proteins encoded by the testis-expressed gene 14 (TEX14) are imperative for spermatogenesis, necessitating intercellular bridges between germ cells. Anomalous expression of TEX14 has also been associated with the proliferation and differentiation of certain tumor cells. Recombinant A disintegrin and metalloprotease 17 (ADAM17) is known as a membrane-bound protease that regulates cellular activities and signal transduction by hydrolyzing various substrate proteins on the cell membrane. We hypothesize that TEX14 and ADAM17 may serve as potential biomarkers influencing the staging, invasion, and metastasis of CRC.

AIM

To probe the correlation between TEX17 and ADAM17 profiles in the CRC tissues of elderly patients and their association with CRC staging, invasion, and metastasis.

METHODS

We gathered data from 86 elderly patients diagnosed pathologically with CRC between April 2020 and December 2023. For each patient, one sample of cancer tissue and one sample of adjacent normal tissue were harvested. Real-time fluorescence quantitative PCR measured the mRNA profiles of TEX14 and ADAM17. Immunohistochemistry ascertained the positivity rates of TEX14 and ADAM17 expressions. Clinical pathological features of neoplasm staging, invasion, and metastasis were collected, and the association between TEX14 and

ADAM17 expressions and clinical pathology was evaluated.

RESULTS

The mRNA and expression profiles of TEX14 and ADAM17 were significantly elevated in CRC tissues. The positivity rates of TEX14 and ADAM17 proteins in CRC tissues were 70.93% and 77.91%, respectively. There were no significant differences in age, sex, pathological type, and tumor diameter between TEX14 and ADAM17-positive and -negative patients. Patients with higher tumor differentiation degree, deeper infiltration and TNM stages ranging from III to IV exhibited higher positivity rates of TEX14 and ADAM17. Patients with lymph node metastasis and distant metastasis showed higher positivity rates of TEX14 and ADAM17 than those without. Positive expressions of TEX14 and ADAM17 were highly correlated with tumor staging, invasion, and metastasis.

CONCLUSION

TEX14 and ADAM17 profiles were significantly elevated in the CRC tissues of elderly patients, and their high expressions were associated with tumor staging, invasion, and metastasis.

Key Words: Elderly patients; Colorectal cancer; TEX14; ADAM17; Staging; Invasion; Metastasis

Core Tip: This research retrospectively harvested clinical data from 86 elderly patients pathologically diagnosed with colorectal cancer to explore the impact of testis-expressed gene 14 (TEX14) and A disintegrin and metalloprotease 17 (ADAM17) expressions on tumor staging, invasion, and metastasis. The outcomes revealed high expressions of TEX14 and ADAM17 in tumor tissues, which were highly correlated with tumor staging, invasion, and metastasis. This suggests that TEX14 and ADAM17 could serve as effective biomarkers for diagnosing and evaluating the progression of CRC in elderly patients.

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INTRODUCTION

Colorectal cancer (CRC) ranks as the third most prevalent lethal malignancy in the world, causing approximately 900000 deaths annually and standing as the second leading cause of cancer-associated deaths worldwide[1,2]. The onset of CRC is linked with advanced age, with elderly individuals being more prone to CRC due to improper dietary habits, declining bodily functions, and factors such as mucosal and muscular atrophy of the colon, which dramatically increase the risk of intestinal mucosal cell mutations, stepping up the possibility of CRC[3]. With the recent advancements in medicine and the development of diagnostic and therapeutic techniques, the detection rate of CRC in its early stages has noticeably increased. Modern screening methods have proven effective in reducing the incidence and mortality rates of CRC[4,5]. Surgery remains the primary treatment modality for early-stage CRC, with tumor resection and lymph node clearance effectively extending the survival period of elderly patients[6]. Nevertheless, in reality, most elderly colorectal cancer patients are often ineligible for surgical treatment due to factors such as advanced age, underlying health conditions, or tumor progression.

Multiple biomarkers assume crucial roles in the occurrence and progression of CRC, as well as in the proliferation, invasion, metastasis, and apoptosis of tumor cells. Testis-expressed gene 14 (TEX14), a critical gene related to reproductive cell stability, influences intercellular bridge function. Its DNA methylation is linked to the development of early-onset familial breast cancer[7,8]. Recombinant A disintegrin and metalloprotease 17 (ADAM17) belongs to the metalloprotease superfamily, located on chromosome 2q24.3, possessing a structural domain with metalloenzyme activity. Tumor necrosis factor-alpha, epidermal growth factor receptor, and other cytokines are its common substrates, participating in the cleavage of various cell surface receptors, influencing cell growth, differentiation, and numerous physiological processes. In recent years, ADAM17 has been discovered to be a central regulatory hub in inflammation, immunity, and malignant tumor diseases, contributing to the occurrence and development of several solid tumors[9]. Wilkinson *et al*[10] found that TEX14 was highly expressed in endometrioid carcinoma tissue based on data from the Cancer Genome Atlas. However, the expression of TEX14 in CRC tissue remains unclear. Additionally, studies have shown that compared to the expression level in normal colonic mucosa, ADAM17 is upregulated in CRC tumor specimens, and inhibiting ADAM17 can significantly suppress tumor cell growth[11].

Based on this, we speculate that TEX14 and ADAM17 may similarly play crucial roles in the formation and progression of CRC in elderly individuals. We harvested cancer tissues and adjacent normal tissues from 86 elderly patients and conducted experimental research to investigate the correlation between TEX14 and ADAM17 expressions in CRC tissues

from elderly individuals and their association with tumor staging, invasion, and metastasis.

MATERIALS AND METHODS

Study participants and inclusion criteria

We retrospectively gathered data from 86 elderly patients diagnosed with CRC through pathological examinations between April 2020 and December 2023 for our research. The study population included 45 males and 41 females, with ages ranging from 60 to 78 (average 66.73 ± standard deviation [SD] 2.12) years. Pathological types were classified as follows: 33 cases of tubular adenocarcinoma, 27 cases of villous adenocarcinoma, and 26 cases of papillary carcinoma. The degrees of tumor differentiation were as follows: 34 cases of high differentiation, 25 cases of moderate differentiation, and 27 cases of poor differentiation. TNM staging consisted of 37 cases of stages I-II and 49 cases of stages III-IV. There were 53 cases with lymph node metastasis and 33 cases without it, as well as 46 cases with distant metastasis and 40 cases without it.

Inclusion criteria: Participants meeting the 8th edition colorectal cancer diagnostic criteria established by the American Joint Committee on Cancer[12] and clinically and pathologically diagnosed with CRC; first-time onset cases; age ≥ 60 years; complete clinical and pathological data; and no prior experiences of radiotherapy, chemotherapy, or other adjuvant treatments.

Exclusion criteria: Individuals with concurrent malignant tumor diseases; those with other digestive system diseases; individuals with hematological diseases or hemorrhagic disorders; those with infectious diseases; individuals with immune deficiencies or systemic immune diseases; or individuals on long-term immunomodulatory therapy.

Sample collection

Tissue samples from the tumors resected from the 86 patients, along with normal intestinal mucosal tissues approximately 5 cm away from the tumors, were harvested. Each sample was preserved in liquid nitrogen for freezing to await further testing. To ensure the accuracy of sample collection and diagnosis, the process was jointly completed by two experienced pathologists.

Clinical data collection

A clinical data collection form was designed to record all patient clinical characteristics, including age, sex, pathological type, tumor diameter, differentiation degree, TNM staging, depth of invasion, lymph node metastasis, and distant metastasis, among other baseline conditions.

Methods

Real-time fluorescent quantitative PCR: Appropriate amounts of tumor tissues and adjacent normal tissues were taken from liquid nitrogen, placed into a homogenizer, and thoroughly ground. After adding 1 mL of Trizol reagent, the samples were left to sit for 5 min at room temperature, followed by total RNA extraction from each tissue sample according to the instructions provided. Denaturing gel electrophoresis was used to evaluate RNA integrity and purity. RNA underwent reverse transcription into cDNA. RT-PCR was performed using the Bio-Rad CFX96 quantitative PCR system and SYBR Green, as instructed by the supplier. The PCR reaction conditions were as follows: 30 sec at 95 °C, 5 sec at 95 °C, 30 sec at 60 °C, and 10 sec at 73 °C for a total of 40 cycles. β-actin was used as the internal control for TEX14 and ADAM17. The relative mRNA profiles of TEX14 and ADAM17 were computed as per the $2^{-\triangle\triangle Ct}$ method. Specific primer sequences are listed in Table 1.

Immunohistochemistry and determination of outcomes: Appropriate amounts of tumor tissues and adjacent normal tissues were taken. After routine embedding in paraffin, the sections were dewaxed and dehydrated in gradient ethanol. After being blocked using 3% H_2O_2 for 10 min to get the endogenous peroxidase inactivated, the sections were treated with 0.01 mol/L sodium citrate buffer and microwaved at a pH of 6.0 for 15 min. The slices, sealed with 5% bovine serum albumin for 20 min, were incubated along with the primary antibodies anti-TEX14 and anti-ADAM17 (purchased from Abcam, Cambridge, United Kingdom) at 4 °C overnight. On the next day, the sections were incubated with goat anti-rabbit IgG (ab109489, 1:50; Abcam) for 20 min at room temperature. After washing with PBS, DAB was used for color development. After hematoxylin counterstaining, the sections were dehydrated and mounted for observation.

With PBS as a control, staining results were determined based on the staining of the tumor cell cytoplasm and cell membrane. Twenty high-power fields (× 400 magnification) were counted for immunohistochemical staining cells. The evaluation criteria were as follows: Staining area: 0 points for staining area below 10%, 1 point for 10%-25%, 2 points for 25%-50%, 3 points for 50%-75%, and 4 points for above 75%; staining intensity: 0 points for no staining, 1 point for pale yellow, 2 points for brownish-yellow, and 3 points for brown. The sum of the scores for staining area and staining intensity was adopted as the total score. A total score of 0 suggested negative, 12 points denoted weak positive (+), 3 points indicated positive (++), and a total score of 5 or more demonstrated strong positive (+++).

Statistical analysis

SPSS 22.0 software (IBM Corp., Armonk, NY, United States) was used for statistical processing and analysis. Quantitative data were presented as mean ± SD and assessed *via* *t*-test. Categorical data were represented as percentages, and χ^2 tests were conducted for comparison. Multifactor analysis was performed using logistic regression analysis, with statistical significance defined as $P < 0.05$.

Table 1 Primer sequences for each gene

Gene	Forward	Reverse
TEX14	ATGTCGGACATCGGAGACTG	CTGGTCTCCAAGTCGAAAG
ADAM17	CTGGCTGGCTCATCACATTC	CATGCCTGTAATCCCAGCAC
β-actin	AGAGCCTCGCCTTTGCCGATCC	CTGGGCCTCGTCGCCCACATA

ADAM17: A disintegrin and metalloprotease 17; TEX14: Testis-expressed gene 14.

RESULTS

Differences in TEX14 and ADAM17 mRNA profiles between CRC tissues and adjacent normal tissues

Compared to adjacent normal tissues, the mRNA profiles of TEX14 and ADAM17 in CRC tissues were significantly elevated ($P < 0.05$), as shown in Table 2 and Figure 1. These findings suggested that the *TEX14* and *ADAM17* genes may play a role in the occurrence and development of CRC, with their high expressions likely accelerating tumor growth and differentiation.

Divergence in TEX14 and ADAM17 protein expressions between CRC and adjacent normal tissues

Among the 86 cases of CRC tissues, 61 were positive for TEX14 and 25 were negative, while 67 cases were positive for ADAM17 and 19 were negative. Among the 86 cases of adjacent normal tissues, 23 cases were positive for TEX14 and 63 were negative, whereas 31 cases were positive for ADAM17 and 55 were negative. The positive profiles of TEX14 and ADAM17 in CRC tissues were significantly higher than those in adjacent normal tissues ($P < 0.05$). The positivity rate of TEX14 protein in CRC tissues was 70.93% (61/86), while the positivity rate of ADAM17 protein was 77.91% (67/86), as displayed in Table 3.

Correlation between TEX14 protein expression and clinical pathology

Patients positive for TEX14 and those negative for TEX14 exhibited no remarkable differences in age, sex, pathological type, and tumor diameter ($P > 0.05$). Among patients with high tumor differentiation, 85.29% were positive for TEX14. In patients with TNM stages III-IV, 81.63% were positive for TEX14. Among patients with lymph node metastasis, 83.13% were positive for TEX14. For patients with infiltration depths of T3 and T4, 80.49% and 87.50%, respectively, were positive for TEX14. Among patients with distant metastasis, 80.43% were positive for TEX14. Hence, we observed that patients with higher tumor differentiation and deeper infiltration displayed higher positivity rates for TEX14 ($P < 0.05$). Patients with TNM stages III-IV had a higher TEX14 positivity rate compared to those with stages I-II ($P < 0.05$). Patients with lymph node metastasis and distant metastasis exhibited higher TEX14 positivity rates than those without ($P < 0.05$), as denoted in Table 4. Our findings confirmed that the profile of the TEX14 protein was correlated with the clinical pathological characteristics of elderly patients with CRC, affecting tumor differentiation, infiltration depth, TNM staging, lymph node metastasis, and distant metastasis.

Correlation between ADAM17 protein expression and clinical pathology

Patients positive and negative for ADAM17 showed no significant differences in age, sex, pathological type, or tumor diameter ($P > 0.05$). Among patients with high tumor differentiation, 91.12% were positive for ADAM17. In patients with TNM stages III to IV, 87.76% tested positive for ADAM17. Among patients with lymph node metastasis, 86.79% were positive for ADAM17. For patients with infiltration depths of T3 and T4, 85.37% and 100%, respectively, were positive for ADAM17. Among patients with distant metastasis, 86.96% tested positive for ADAM17. Hence, patients with higher tumor differentiation and deeper infiltration exhibited higher positivity rates for ADAM17 ($P < 0.05$). Patients with TNM stages III-IV had a higher ADAM17 positivity rate than those with stages I-II ($P < 0.05$). Patients with lymph node metastasis and distant metastasis displayed heightened ADAM17 positivity rates than those without ($P < 0.05$), as illustrated in Table 5. From these results, it can be inferred that the expression of ADAM17 protein is linked to the clinical pathological characteristics of elderly patients with CRC. Moreover, positive expression of ADAM17 influences tumor differentiation, infiltration depth, TNM staging, lymph node metastasis, and distant metastasis.

Relationship between TEX14 and ADAM17 profiles and tumor staging, invasion, and metastasis

Using tumor TNM staging, invasion degree, and metastasis status of elderly patients with CRC as dependent variables, and TEX14 and ADAM17 expression as independent variables, the binary variable assignment table is illustrated in Table 6. Multiple logistic regression analysis was performed to examine the relationship between TEX14 and ADAM17 expressions and tumor staging, invasion, and metastasis. As evidenced by our research data, TEX14 positive expression was associated with higher TNM staging (OR = 3.343, 95%CI: 1.211-9.228, $P < 0.05$), deeper invasion (OR = 14.924, 95%CI: 2.152-103.491, $P < 0.05$), lymph node metastasis (OR = 5.018, 95%CI: 1.195-21.067, $P < 0.05$), and distant metastasis (OR = 6.203, 95%CI: 1.246-30.884, $P < 0.05$). Similarly, positive expression of ADAM17 was correlated with higher TNM staging (OR = 4.963, 95%CI: 1.546-15.930, $P < 0.05$), deeper invasion (OR = 6.593, 95%CI: 1.366-31.813, $P < 0.05$), lymph node metastasis (OR = 2.659, 95%CI: 1.067-6.628, $P < 0.05$), as well as distant metastasis (OR = 7.980, 95%CI: 1.651-38.584, $P <$

Table 2 Differences in TEX14 and ADAM17 mRNA profiles between colorectal cancer tissues and adjacent normal tissues

Group	*n*	TEX14 mRNA	ADAM17 mRNA
CRC tissues	86	1.61 ± 0.23	1.82 ± 0.29
Adjacent normal tissues	86	0.98 ± 0.13	1.00 ± 0.12
t value		22.114	24.230
P value		< 0.001	< 0.001

Data are mean ± standard deviation. ADAM17: A disintegrin and metalloprotease 17; CRC: Colorectal cancer; TEX14: Testis-expressed gene 14.

Table 3 TEX14 and ADAM17 protein profiles in colorectal cancer and adjacent normal tissues

Group	*n*	TEX14				ADAM17			
		(-)	(+)	(++)	(+++)	(-)	(+)	(++)	(+++)
CRC tissues	86	25 (29.07)	20 (23.26)	29 (33.72)	12 (13.95)	19 (22.09)	31 (36.04)	27 (31.40)	9 (10.47)
Adjacent normal tissues	86	63 (73.26)	17 (19.76)	6 (6.98)	0 (0)	55 (63.95)	18 (20.93)	13 (15.12)	0 (0)
χ^2 value		43.767				34.863			
P value		< 0.001				< 0.001			

Data are *n* (%). ADAM17: A disintegrin and metalloprotease 17; CRC: Colorectal cancer; TEX14: Testis-expressed gene 14.

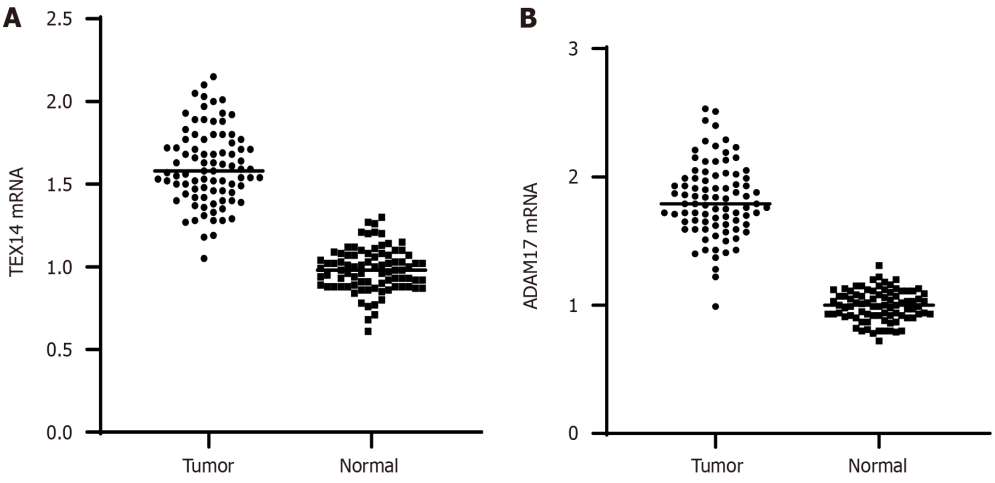

Figure 1 TEX14 (A) and ADAM17 (B) mRNA profiles in 86 cases of colorectal cancer tissues and adjacent normal tissues. ADAM17: A disintegrin and metalloprotease 17; TEX14: Testis-expressed gene 14.

0.05), as shown in Table 7. This indicates that high expressions of TEX14 and ADAM17 significantly influence tumor staging, invasion, and metastasis in elderly patients with CRC, promoting the malignant progression of tumors and contributing to advanced tumor TNM staging, aggravated invasion, and metastasis.

DISCUSSION

Due to the lack of specific symptoms in the early stages of CRC, most elderly patients are diagnosed at an advanced stage. This results in late tumor staging, deeper invasion, and conventional surgical treatment options often failing to achieve desirable outcomes, high surgical risks, poor postoperative recovery, and unfavorable prognosis. In clinical practice, it is necessary to combine the clinical and pathological characteristics of elderly patients to enhance treatment efficacy through adjuvant therapies such as chemotherapy, radiotherapy, and targeted therapy[13-15]. In advanced stages of CRC in elderly patients, tumor cell proliferation is rapid, and invasion and metastasis exacerbate, accompanied by uncontrolled apoptosis. Studies have suggested that various genes such as *STC1*, *AKR1B1*, and *EMP1* are overexpressed in invasive tumor clusters of CRC, affecting local invasion and patient prognosis[16]. Identifying biomarkers associated

Table 4 Association between the protein profile of TEX14 and clinical pathology

Pathological features		*n*	TEX14		X^2 value	*P* value
			Positive, *n* = 61	Negative, *n* = 25		
Age	≥ 65 years	54	36 (66.67)	18 (33.33)	1.279	0.258
	< 65 years	32	25 (78.13)	7 (21.88)		
Sex	Male	47	35 (74.47)	12 (25.53)	0.629	0.428
	Female	39	26 (66.67)	13 (33.33)		
Pathological type	Tubular adenocarcinoma	33	23 (69.70)	10 (30.30)	0.715	0.699
	Villous adenocarcinoma	27	18 (66.67)	9 (33.33)		
	Papillary carcinoma	26	20 (76.92)	6 (23.08)		
Tumor diameter	≥ 3 cm	46	30 (65.22)	16 (34.78)	1.565	0.211
	< 3 cm	40	31 (77.50)	9 (22.50)		
Differentiation degree	Low differentiation	27	15 (55.56)	12 (44.44)	6.602	0.037
	Moderate differentiation	25	17 (68.00)	8 (32.00)		
	High differentiation	34	29 (85.29)	5 (14.71)		
TNM staging	Stages I-II	37	21 (56.76)	16 (43.24)	6.327	0.012
	Stages III-IV	49	40 (81.63)	9 (18.37)		
Lymph node metastasis	Presence	53	43 (83.13)	10 (18.87)	6.972	0.008
	Absence	33	18 (54.55)	15 (45.45)		
Infiltration depth	T1 + T2	37	21 (56.76)	16 (43.24)	6.486	0.039
	T3	41	33 (80.49)	8 (19.51)		
	T4	8	7 (87.50)	1 (12.5)		
Distant metastasis	Presence	46	37 (80.43)	9 (19.57)	4.333	0.037
	Absence	40	24 (60.00)	16 (40.00)		

Data are *n* (%). TEX14: Testis-expressed gene 14.

with TNM staging, invasion, and metastasis in elderly patients with CRC is essential for enhancing tumor screening and disease assessment. This greatly aids in improving prognosis and increasing the expected survival duration for elderly patients.

TEX14, as a regulator of the PLK1 protein, is an important regulatory mediator of kinetochore structure, function, and chromosome segregation fidelity during mitosis[17]. Recent studies have revealed that TEX14-IT1 mediates the pro-proliferative and anti-apoptotic functions of transforming growth factor-beta in ovarian granular cells. This mechanism involves inducing the transcription of TEX14-IT1 in an AMAD4-dependent manner, exerting epigenetic regulatory effects [18]. Furthermore, in cancer, the TEX14 rs302864 site can interact with SEPT4 rs758377, influencing specific molecular subtypes of breast tumors, thereby augmenting the risk of breast cancer[19]. ADAM17, as a type of multi-domain transmembrane glycoprotein, participates in the formation and release of pro-tumor progression-related ligands, thus affecting the malignant progression of various tumors[20-22]. Previous studies have discovered that the expression level of ADAM17 is related to the ability of human umbilical vein endothelial cells to form capillary-like networks when co-cultured with fibroblasts in three-dimensional matrix gel and scaffolds. ADAM17 can participate in angiogenesis by modulating the activation of matrix metalloproteinase 2[23,24]. In CRC, FHL2 inhibits ADAM17 activity by regulating its plasma membrane localization. The interplay between FHL2 and ADAM17 in malignant colonic epithelial cells forms a complex that influences the occurrence and development of CRC[25].

Currently, there is scarce research on the functions of TEX17 and ADAM17 in the staging, invasion, and metastasis of CRC. To address this gap, our experiment explored these aspects. We found that TEX14 and ADAM17 expression levels in the tumor tissues of elderly patients with CRC were significantly higher than in adjacent normal tissues. High expression of TEX14 and ADAM17 was associated with tumor differentiation, TNM staging, invasion depth, lymph node metastasis, and distant metastasis in elderly patients, establishing them as independent risk factors affecting the staging, invasion, and metastasis of tumors. Our findings align with those of Kumar *et al*[26], who found that multiple biomarkers such as SVIP, BEND3, and TEX14 were abnormally expressed in breast cancer and could serve as efficacious indicators for early, non-invasive diagnosis and prognosis. Additionally, a study by Li *et al*[27] confirmed that exosomal ADAM17

Table 5 Correlation between ADAM17 protein expression and clinical pathology

Pathological characteristic		*n*	ADAM17		χ^2 value	*P* value
			Positive, *n* = 67	Negative, *n* = 19		
Age	≥ 65 years	54	44 (81.48)	10 (18.52)	1.077	0.299
	< 65 years	32	23 (71.88)	9 (28.13)		
Sex	Male	47	39 (82.98)	8 (17.02)	1.549	0.213
	Female	39	28 (71.79)	11 (28.21)		
Pathological type	Tubular adenocarcinoma	33	27 (81.82)	6 (18.18)	1.308	0.520
	Villous adenocarcinoma	27	19 (70.37)	8 (29.63)		
	Papillary carcinoma	26	21 (80.77)	5 (19.23)		
Tumor diameter	≥ 3 cm	46	38 (82.61)	8 (17.39)	1.270	0.260
	< 3 cm	40	29 (72.50)	11 (27.50)		
Differentiation degree	Low differentiation	27	20 (74.07)	7 (25.93)	10.079	0.006
	Moderate differentiation	25	15 (60.00)	10 (40.00)		
	High differentiation	34	32 (94.12)	2 (5.88)		
TNM staging	Stages I-II	37	24 (64.86)	13 (35.14)	6.418	0.011
	Stages III-IV	49	43 (87.76)	6 (12.24)		
Lymph node metastasis	Presence	53	46 (86.79)	7 (13.21)	6.336	0.012
	Absence	33	21 (63.64)	12 (36.36)		
Infiltration degree	T1 + T2	37	24 (64.86)	13 (35.14)	7.250	0.027
	T3	41	35 (85.37)	6 (14.63)		
	T4	8	8 (100.00)	0 (0)		
Distant metastasis	Presence	46	40 (86.96)	6 (13.04)	4.706	0.030
	Absence	40	27 (67.50)	13 (32.50)		

Data are *n* (%). ADAM17: A disintegrin and metalloprotease 17.

could accelerate the formation of pre-metastasis niches by strengthening CRC vascular permeability and promoting cancer metastasis. Previous studies may have already revealed the key roles of these two genes in the development of CRC, possibly associated with tumor growth, invasion, and metastasis. By comparing our research results, the exact mechanisms of action of these genes in the pathophysiological processes of CRC can be further validated. The outcomes of our experiment may be related to the following reasons: TEX14 may suppress apoptosis of tumor cells endogenously by affecting the mitosis process of CRC cells, accelerating cell proliferation, invasion, and metastasis, thereby bolstering CRC malignancy[28]. Furthermore, ADAM17, as a mediator in cell-matrix interactions, interacts with integrin α5, degrading the cell basement membrane and extracellular matrix. This interaction reduces the levels of adhesion molecules on the surface of CRC cells, impairing their function in cancer cell invasion and metastasis[29], ultimately exacerbating the malignant progression of tumors.

The clinical significance of these research findings is very important. By further investigating the relationship between the expression of TEX14 and ADAM17 in patients with CRC and metastasis, these genes could be utilized as potential therapeutic targets, providing a new direction for the treatment of CRC. However, this work also has certain limitations and shortcomings. Firstly, it is a retrospective study, which inherently has limitations. All data and information are derived from historical data of cases, which may result in incomplete information or selection bias, thus affecting the experimental findings. Additionally, this study included only 86 patients, which is a relatively small size, and all samples were sourced from a single hospital, which may introduce institutional bias, influencing the external validity and generalizability of the study outcomes. In the future, we will consider using carefully designed prospective studies combined with standardized data sampling to provide more robust evidence for our experimental results.

CONCLUSION

Overall, our findings corroborate the indispensable role of TEX14 and ADAM17 in the clinical diagnosis and prognosis assessment of elderly individuals with CRC. They can serve as effective biomarkers for predicting disease progression

Table 6 Binary variable assignment

Variable	Assignment	Outcomes
TNM staging	Stages I-II	0
	Stages III-III	1
Invasion	Infiltration depths T1 + T2	0
	Infiltration depths T3 + T4	1
Lymph node metastasis	Presence	1
	Absence	0
Distant metastasis	Presence	1
	Absence	0
TEX14	Positive	1
	Negative	0
ADAM17	Positive	1
	Negative	0

ADAM17: A disintegrin and metalloprotease 17; TEX14: Testis-expressed gene 14.

Table 7 Correlation between TEX14 and ADAM17 profiles and tumor staging, invasion, and metastasis

C	TEX14						ADAM17					
	B	SE	Wald	OR	95%CI	*P* value	β	SE	Wald	OR	95%CI	*P* value
TNM staging	1.207	0.518	5.429	3.343	1.211-9.228	0.020	1.602	0.595	7.249	4.963	1.546-15.930	0.007
Invasion	2.703	0.988	7.485	14.924	2.152-103.491	0.006	1.886	0.803	5.516	6.593	1.366-31.813	0.019
Lymph node metastasis	1.613	0.732	4.856	5.018	1.195-21.067	0.028	0.978	0.466	4.405	2.659	1.067-6.628	0.036
Distant metastasis	1.825	0.819	4.965	6.203	1.246-30.884	0.026	2.077	0.804	6.674	7.980	1.651-38.584	0.010

ADAM17: A disintegrin and metalloprotease 17; TEX14: Testis-expressed gene 14.

and prognosis in patients. In clinical practice, when treating elderly patients with CRC, it is essential to focus not only on common prognostic indicators and pathological results but also to strengthen the monitoring of TEX14 and ADAM17 markers. Future clinical research can further validate the value of these genes as potential diagnostic markers or therapeutic targets, providing new insights and possibilities for developing more effective treatment strategies.

FOOTNOTES

Author contributions: Chen G designed the research study; Chen G and Cong LH performed the research; Chen G, Gu CJ, and Li P analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of The Affiliated People's Hospital of Ningbo University (Approval No. 2020-NB-021032).

Informed consent statement: Patients were not required to provide informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient agreed to the treatment through written consent.

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ORIGINAL ARTICLE

Retrospective Study

Assessment of early factors for identification or prediction severe acute pancreatitis in pregnancy

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Abstract

BACKGROUND

Acute pancreatitis in pregnancy (APIP) is a rare and serious condition, and severe APIP (SAPIP) can lead to pancreatic necrosis, abscess, multiple organ dysfunction, and other adverse maternal and infant outcomes. Therefore, early identification or prediction of SAPIP is important.

AIM

To assess factors for early identification or prediction of SAPIP.

METHODS

The clinical data of patients with APIP were retrospectively analyzed. Patients were classified with mild acute pancreatitis or severe acute pancreatitis, and the clinical characteristics and laboratory biochemical indexes were compared between the two groups. Logical regression and receiver operating characteristic curve analyses were performed to assess the efficacy of the factors for identification or prediction of SAPIP.

RESULTS

A total of 45 APIP patients were enrolled. Compared with the mild acute pancreatitis group, the severe acute pancreatitis group had significantly increased ($P < 0.01$) heart rate (HR), hemoglobin, neutrophil ratio (NEUT%), and neutrophil–lymphocyte ratio (NLR), while lymphocytes were significantly decreased ($P < 0.01$). Logical regression analysis showed that HR, NEUT%, NLR, and lym-

phocyte count differed significantly ($P < 0.01$) between the groups. These may be factors for early identification or prediction of SAPIP. The area under the curve of HR, NEUT%, NLR, and lymphocyte count in the receiver operating characteristic curve analysis was 0.748, 0.732, 0.821, and 0.774, respectively. The combined analysis showed that the area under the curve, sensitivity, and specificity were 0.869, 90.5%, and 70.8%, respectively.

CONCLUSION
HR, NEUT%, NLR, and lymphocyte count can be used for early identification or prediction of SAPIP, and the combination of the four factors is expected to improve identification or prediction of SAPIP.

Key Words: Severe acute pancreatitis in pregnancy; Early identification factors; Early predictive factors; Clinical features; Laboratory biochemical index

Core Tip: This retrospective study explored factors for early identification or prediction of severe acute pancreatitis in pregnancy (SAPIP). A total of 45 APIP patients were enrolled. Logistic regression analysis showed that heart rate, neutrophil ratio, neutrophil–lymphocyte ratio, and lymphocyte count were significantly correlated with SAPIP. These four indexes showed valuable area under the curve, sensitivity, and specificity through receiver operating characteristic curve analysis. These results suggested that heart rate, neutrophil ratio, neutrophil-lymphocyte ratio, and lymphocyte count can be used for early identification or prediction of SAPIP.

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INTRODUCTION

Acute pancreatitis in pregnancy (APIP) is a rare but serious condition, and the incidence is reported to be between 1/12000 and 1/1000[1-3]. Although APIP is rare in the clinic, it may be associated with high maternal mortality and fetal loss[4-6], and it has been shown increasing attention by researchers.

Previous studies have shown that severe APIP (SAPIP) is significantly associated with a high risk of maternal and fetal death[7,8]; therefore, early identification and prediction of SAPIP, as well as timely and appropriate management, are critical to fetal and maternal prognosis. There are currently several scoring systems used to assess AP severity[9]. Many hematological changes occur in women during pregnancy, so APIP has some special clinical features in addition to the characteristics of general pancreatitis. Therefore, these scores may not accurately assess and predict the severity of APIP [10,11]. Better indicators for early identification and prediction of APIP severity are needed. Some studies suggested that the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, erythrocyte distribution width-platelet ratio, γ-glutamyl transpeptidase, lipase, high-density lipoprotein, platelet volume, lactate dehydrogenase, triglyceride, and cholesterol may be predictors of APIP[12-15]. However, there are few reports on the early identification and prediction of SAPIP.

Based on 45 clinical cases of APIP from the Department of Critical Care Medicine, Maternal and Child Health Hospital of Hubei Province and Department of Biliary-Pancreatic Surgery, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, this retrospective study identified multiple factors associated with SAPIP. Clinical parameters were compared between patients with mild APIP (MAPIP) and those with SAPIP. These are expected to facilitate the timely identification and prediction of SAPIP.

MATERIALS AND METHODS

Study subjects and definitions

A retrospective study was conducted on APIP patients admitted to the Department of Critical Care Medicine, Maternal and Child Health Hospital of Hubei Province and Department of Biliary–Pancreatic Surgery, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology from 2017 to 2020. Due to the difficulty in obtaining data for patients before admission, data were only collected for the first examination within 24 h after hospitalization. Information on maternal age, gestational age at onset, potential causes of AP, clinical manifestations and complications, laboratory data, and maternal and fetal outcomes were collected from patient medical records.

We defined APIP as AP that occurred during pregnancy and the 42-d postpartum period. Diagnosis of AP needs to meet at least two of the following three characteristics on the basis of the Revised Atlanta criteria[16]: (1) Acute persistent epigastric pain; (2) Serum amylase and/or lipase increased by > 3 times the upper limit of normal; and (3) Abdominal imaging findings consistent with AP. Based on the Revised Atlanta criteria[16], AP was classified into three categories according to severity: (1) Mild AP (MAP), pancreatitis without organ dysfunction or systemic complications; (2) Moderately severe AP (MSAP), pancreatitis with persistent organ dysfunction or local/systemic complications within 48 h of starting treatment; and (3) Severe AP (SAP), persistent pancreatitis dysfunction or local/systemic complications.

Patients with chronic pancreatitis and patients with missing data were excluded from the study. We enrolled 45 patients with APIP. Due to the small number of cases of MSAP in this study, patients were divided into two groups: MAP and SAP (including MSAP and SAP). There were 24 cases of MAP and 21 cases of SAP. The study was approved by the Ethics Committee of Hubei Maternal and Child Health Care Hospital and Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology. Technical records. Data did not include potential patient identifying information and therefore did not require informed consent.

Statistical analysis

SPSS 17.0 was used for data analysis. The measurement data of normal distribution were expressed as mean ± standard deviation, and *t* test of two independent samples was used for comparison between groups. Measurement data with non-normal distribution were expressed as median (interquartile range), and the nonparametric Mann–Whitney *U* test was used for comparison between groups. The numerical data were expressed as frequency, and groups were compared by Fisher's exact test. Logistic regression analysis was performed on the variables with significant differences between the groups to analyze the factors associated with SAPIP. Receiver operating characteristic curve (ROC) was plotted to evaluate the predictive efficiency of each indicator.

RESULTS

General clinical features

The 45 patients had a mean age of 30.0 ± 3.8 years (range: 22-37 years). According to the etiology, there were 18 cases (40.0%) of hypertriglyceridemia, 11 cases (24.44%) of cholelithiasis (24.44%), and 16 cases (35.56%) of other diseases. APIP patients included 4 cases (10.26%) in the first trimester, 9 cases (20.51%) in the second trimester, and 32 cases (69.23%) in the third trimester. There were no maternal deaths, but fetal loss occurred in 6 cases. In the initial hospitalization, 13 cases were diagnosed as severe; 4 cases had acute respiratory distress syndrome, and 5 cases had shock symptoms. Acidosis and renal dysfunction occurred in 2 cases and liver failure in 2 cases. Eight cases became severe after hospitalization; 3 cases had renal dysfunction, 3 cases had pancreatic hemorrhage and necrosis, and 2 cases had acute respiratory distress syndrome and liver failure. Due to the small sample size, there may have been errors in individual analysis, so the two groups were studied as a whole in the following study.

Differences in general clinical features between MAPIP and SAPIP

We mainly compared the general clinical characteristics of MAPIP with SAPIP, including underlying etiology, pregnancy stage, age, heart rate (HR), and blood pressure. There were no significant differences in underlying etiology and pregnancy stage between the two groups (Tables 1 and 2). There were also no significant differences in age and blood pressure (Table 3). HR in the severe group was significantly higher than in the mild group ($P < 0.01$) (Table 3).

Differences in laboratory biochemical indicators between MAPIP and SAPIP

Whole blood was collected to compare the laboratory biochemical indicators. Hemoglobin and neutrophil ratio (NEUT%) in the SAPIP group were significantly higher than in the MAPIP group ($P < 0.01$) (Table 4). The total number of lymphocytes in the SAPIP group was significantly lower than that in the MAPIP group ($P < 0.01$). NLR in the SAPIP group was significantly higher than in the MAPIP group ($P < 0.01$) (Table 4).

Assessment of factors associated with SAPIP

Logistic regression analysis was performed on HR, hemoglobin, NEUT%, lymphocyte count, and NLR, which were significantly different between the MAPIP and SAPIP groups. HR, NEUT%, lymphocyte count, and NLR were significantly correlated with severity of APIP ($P < 0.01$), but hemoglobin was not ($P > 0.01$) (Table 5). ROC curves showed the early recognition or predictive efficiency of each relevant factor (Table 6 and Figure 1A). NLR had the largest area under the curve (AUC) (0.821). To evaluate whether their combination was more effective, ROC curve analysis was performed on the four factors. AUC for combined detection was 0.869, sensitivity was up to 90.5%, and specificity was up to 70.8% (Figure 1B).

DISCUSSION

We reported the value of combining detection of vital signs and laboratory biochemical indicators in early identification or prediction of SAPIP after hospitalization. Compared with the MAPIP group, HR, NEUT%, and NLR were significantly higher in the SAPIP group, while lymphocyte count was significantly reduced in the SAPIP group. To assess whether

Table 1 Differences in etiology

Etiology	MAPIP, *n* = 24	SAPIP, *n* = 21	Test value	*P* value
Hypertriglyceridemia	6	12	χ^2 = 4.890	0.087[1]
Biliary	7	4		
Other causes	11	5		

[1]Pearson's χ^2 test. MAPIP: Mild acute pancreatitis in pregnancy; SAPIP: Severe acute pancreatitis in pregnancy.

Table 2 Differences during pregnancy stage

Pregnancy stage	MAPIP, *n* = 24	SAPIP, *n* = 21	*P* value
First trimester	2	2	0.258[1]
Second trimester	7	2	
Late trimester	15	17	

[1]Fisher's exact test. MAPIP: Mild acute pancreatitis in pregnancy; SAPIP: Severe acute pancreatitis in pregnancy.

Table 3 Differences in age, heart rate, and blood pressure

Factors	MAPIP, *n* = 24	SAPIP, *n* = 21	Test value	*P* value
Age in yr	28.82 ± 4.50	30.40 ± 4.10	*t* = 0.521	0.605[1]
Heart rate in bpm	88.0 (19.75)	120.0 (40.0)	z = -2.849	0.004[2]
Systolic blood pressure in mmHg	115.67 ± 11.89	119.57 ± 11.82	*t* = -1.102	0.277[1]
Diastolic blood pressure in mmHg	73.21 ± 9.48	76.24 ± 9.16	*t* = -1.087	0.283[1]

Data are *n* (%).
[1]*T*-test of two independent samples.
[2]Mann–Whitney nonparametric test.
MAPIP: Mild acute pancreatitis in pregnancy; SAPIP: Severe acute pancreatitis in pregnancy.

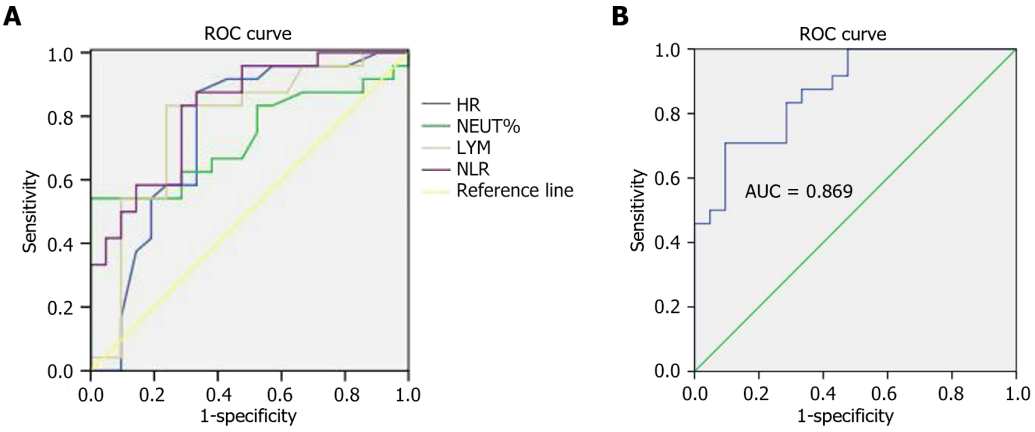

Figure 1 Specificity and sensitivity of heart rate, neutrophil ratio, lymphocyte count, and neutrophil-lymphocyte ratio were analyzed by receiver operating characteristic curve. A: Analysis of individual factors; B: Analysis of combination of factors. HR: Heart rate; LYM: Lymphocyte count; NEUT%: Neutrophil ratio; NLR: Neutrophil–lymphocyte ratio; ROC: Receiver operating characteristic.

Table 4 Comparison of the first laboratory biochemical indicators after admission

Factor	MAPIP, *n* = 24	SAPIP, *n* = 21	Test value	*P* value
RBC as × 10^{12}	3.53 ± 0.48	3.95 ± 0.75	*t* = -2.275	0.028
HCT	33.40 ± 5.65	36.99 ± 5.14	*t* = -2.219	0.032
HGB in g/L	110.67 ± 17.49	127.71 ± 22.68	*t* = -3.003	0.004
RDW	13.45 (1.12)	13.80 (2.35)	*z* = -1.298	0.194
WBC as × 10^{9}	12.42 ± 5.02	15.08 ± 5.55	*t* = -1.688	0.099
NEUT as × 10^{9}	11.18 ± 4.81	14.66 ± 4.81	*t* = -2.422	0.02
NEUT%	83.84 ± 8.44	90.14 ± 3.52	*t* = -3.183	0.003
LYM as × 10^{9}	1.23 (0.46)	0.58 (0.51)	*z* = -3.141	0.002
NLR	8.12 (9.80)	27.43 (25.61)	*z* = -3.686	0
TG in mmol/L	2.63 (6.80)	19.05 (31.49)	*z* = -2.207	0.027
TC in mmol/L	5.26 (2.41)	14.32 (14.29)	*z* = -1.615	0.106
Ca in mmol/L	2.13 (0.15)	2.04 (0.38)	*z* = -0.854	0.393
AMY in U/L	387 (1450.00)	588 (763.60)	*z* = -0.375	0.707
BUN in mmol/L	3.06 (1.12)	2.16 (2.75)	*z* = -0.797	0.426
SCR in mg/dL	47.66 (13.17)	47.45 (17.55)	*z* = 0.046	0.946
GPT in U/L	8.90 (16.00)	8.30 (33.10)	*z* = -0.194	0.846
GOT (U/L)	17.85 (21.73)	18.00 (28.50)	*z* = -0.546	0.585
DBIL in μmol/L	3.25 (2.43)	3.40 (4.45)	*z* = -0.046	0.964
IBIL in μmol/L	7.42 (3.80)	7.46 (4.37)	*z* = -0.032	0.975

AMY: Amylase; BUN: Blood urea nitrogen; DBIL: Direct bilirubin; GOT: Glutamic oxaloacetic transaminase; GPT: Glutamic pyruvic transaminase; HCT: Hematocrit value; HGB: Hemoglobin; IBIL: Indirect bilirubin; LYM: Lymph; MAPIP: Mild acute pancreatitis in pregnancy; NEUT: Neutrophil; NEUT%: Neutrophil ratio; NLR: Neutrophil–lymphocyte ratio; RBC: Red blood cell; RDW: Red blood cell distribution width; SAPIP: Severe acute pancreatitis in pregnancy; SCR: Serum creatinine; TC: Total cholesterol; TG: Triglyceride; WBC: White blood cell.

Table 5 Logistic regression analysis of related factors

Factor	OR	95%CI	*P* value
Heart rate in bpm	1.052	1.016–1.090	0.004
Hemoglobin in g/L	1.046	1.009–1.048	0.014
NEUT%	1.179	1.043–1.333	0.009
LYM as × 10^{9}	0.095	0.019–0.483	0.005
NLR	1.121	1.045–1.202	0.001

CI: Confidence interval; LYM: Lymphocyte count; NEUT%: Neutrophil ratio; NLR: Neutrophil-lymphocyte ratio; OR: Odds ratio.

these indicators can be used as factors for identification or prediction of SAPIP, ROC analysis was performed for HR, NEUT%, lymphocyte count, and NLR. The AUC for combined analysis of the four indicators was 0.869, sensitivity was 90.5%, and specificity was 70.8%. Therefore, combined detection of the four indicators is helpful for early identification or prediction of SAPIP.

SAPIP seriously threatens the health and life of pregnant women and fetuses[17-19]. Due to the lack of indicators for early identification or prediction of SAPIP, most previous studies have determined some laboratory detection indicators for predicting APIP by comparing APIP patients with normal pregnant women[13,14]. Some studies compared SAP with MAP and MSAP to explore the indicators related to APIP severity, but only laboratory data were selected for the indicators[20,21]. Our study also included vital signs such as HR and blood pressure, which could have made the assessment more comprehensive.

Table 6 Assessment of the effectiveness of relevant factors

Factors	AUC	95%CI	*P* value	Cutoff	Sensitivity, %	Specificity, %
HR in bpm	0.748	0.593-0.903	0.004	107.000	66.7	87.5
NEUT%	0.732	0.582-0.882	0.008	84.300	100	54.2
LYM as $\times 10^9$	0.774	0.628-0.920	0.002	0.875	83.3	76.2
NLR	0.821	0.700-0.943	0.000	17.890	71.4	83.3

AUC: Area under the curve; CI: Confidence interval; HR: Heart rate; NEUT%: Neutrophil ratio; LYM: Lymphocyte count; NLR: Neutrophil–lymphocyte ratio.

Many studies have shown that lymphocytes are involved in the inflammatory response of AP[22-25]. Studies showed that the lymphocyte DNA damage in AP patients was significantly higher than that in the control groups, especially the high level of lymphocyte DNA damage in SAP patients[26]. Patients with persistently low lymphocyte counts in the early stage of AP are more likely to develop infectious pancreatic necrosis (IPN), which can predict the severity of AP and the development of IPN, and it is important for early diagnosis and timely intervention[27]. The role of the lymphocyte count in predicting APIP has not been reported previously. In our study, we reported a significantly reduced lymphocyte count with a higher AUC (0.774), second only to NLR. If the threshold value was 0.875 × 10^9, the sensitivity was 83.3%, suggesting that lymphocyte count could be one of the best predictors of SAPIP.

Although the detailed mechanism of the relationship between neutrophils and AP has not been elucidated, some studies suggest that neutrophils play an important role in the exacerbation of AP, possibly through the neutrophilic extracellular trap pathway[28-30]. Studies have shown that elevated neutrophils are associated with complications such as pancreatic infection and necrosis and pseudocyst formation and can be used as a predictor of AP complications[31]. The critical value for predicting the occurrence of IPN is > 9.47 × 10^9, with sensitivity up to 69.09% and specificity up to 60.74%[32]. In our study, we reported that blood neutrophil count was correlated with APIP severity, and the best diagnostic threshold for predicting severe pancreatitis was 84.30%, with sensitivity up to 100% and specificity up to 54.20%, which could be used as one of predictors of SAPIP.

NLR is a more comprehensive biomarker that uses neutrophil and lymphocyte counts to respond quickly to the extent of inflammation progression and serves as a useful predictor for identifying the severity of AP[33-36]. Meta-analysis showed that the AUC of NLR for predicting the severity of pancreatitis was 0.82, indicating that it had a moderately high predictive value[34]. In APIP, İlhan *et al*[12] reported in 2015 that NLR may have a role in prediction of disease severity with a sensitivity of 78.6% and specificity of 62.1%. However, the predictive value of NLR reported in the literature is inconsistent[37]. Some authors have suggested that NLR alone may not be a true indicator of the severity of AP because it is affected by treatment drugs and waiting period prior to analysis[37]. In our study, NLR could be used as a valuable factor for identification or prediction of SAPIP with sensitivity of 71.40% and specificity of 83.30%.

SAP can cause tachycardia through metabolic disorders, vagal reflex, hemodynamic instability, myocarditis, and other mechanisms[38]. Tachycardia includes sinus tachycardia, supraventricular tachycardia, and ventricular tachycardia; among which, sinus tachycardia is the most common[39]. The role of HR in early recognition/prediction of SAP has not been reported. In our study, HR in the SAPIP group was significantly higher than in the MAPIP group. The best diagnostic threshold for predicting severe pancreatitis was 107 bpm, sensitivity was 66.7%, and specificity was 87.5%. It could be used for identification or prediction of SAPIP.

Our study had several limitations. First, we included only patients with complete APIP records at the two centers, and some patients who were not admitted were excluded from the analysis. Therefore, a larger, multicenter prospective study is needed to validate these results. Second, due to the small number of MSAP cases, their inclusion in the SAP group may have biased the data of the SAP group. Third, due to the small size of the overall sample, the time of onset of severe disease was not classified, so early identification and prediction were not analyzed separately.

CONCLUSION

We identified HR, NEUT%, and NLR as independent factors for early identification or prediction of SAPIP. Combined detection with the four factors can help improve early prediction and identification, which can help to determine treatment management and improve outcomes.

FOOTNOTES

Author contributions: Tian R and Shi CJ conceptualized and designed the research; Mei LF, Gan Q, Hu J, and Li YX screened patients and acquired clinical data; Mei LF, Tian R, and Shi CJ performed the data analysis; Mei LF, Tian R, and Shi CJ wrote the paper; All authors read and approved the final manuscript. Mei LF acquired clinical data, performed data analysis, and prepared the first draft of the manuscript. She has made crucial and indispensable contributions towards the completion of the project and thus qualified as one of the

first authors of the paper. Both Tian R and Shi CJ have played important and indispensable roles in the research design, data interpretation, and manuscript preparation as the co-corresponding authors. Shi CJ conceptualized, designed, and supervised the whole process of the project. He searched the literature and revised and submitted the early version of the manuscript. Tian R was instrumental and responsible for data re-analysis and re-interpretation, figure plotting, the comprehensive literature search, and preparation and submission of the current version of the manuscript. This collaboration between Tian R and Shi CJ was crucial for the publication of this manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology and the Ethics Committee of Maternal and Child Health Hospital of Hubei Province (Approval No.: TJ-IRB202404002 and 2023IEC097).

Informed consent statement: Technical records and data did not include potential patient identifying information and therefore did not require informed consent.

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

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Application value of machine learning models in predicting intraoperative hypothermia in laparoscopic surgery for polytrauma patients

Kun Zhu, Zi-Xuan Zhang, Miao Zhang

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Abstract

BACKGROUND

Hypothermia during laparoscopic surgery in patients with multiple trauma is a significant concern owing to its potential complications. Machine learning models offer a promising approach to predict the occurrence of intraoperative hypothermia.

AIM

To investigate the value of machine learning model to predict hypothermia during laparoscopic surgery in patients with multiple trauma.

METHODS

This retrospective study enrolled 220 patients who were admitted with multiple injuries between June 2018 and December 2023. Of these, 154 patients were allocated to a training set and the remaining 66 were allocated to a validation set in a 7:3 ratio. In the training set, 53 cases experienced intraoperative hypothermia and 101 did not. Logistic regression analysis was used to construct a predictive model of intraoperative hypothermia in patients with polytrauma undergoing laparoscopic surgery. The area under the curve (AUC), sensitivity, and specificity were calculated.

RESULTS

Comparison of the hypothermia and non-hypothermia groups found significant differences in sex, age, baseline temperature, intraoperative temperature, duration of anesthesia, duration of surgery, intraoperative fluid infusion, crystalloid infusion, colloid infusion, and pneumoperitoneum volume ($P < 0.05$). Differences between other characteristics were not significant ($P > 0.05$). The results of the logistic regression analysis showed that age, baseline temperature, intraoperative temperature, duration of anesthesia, and duration of surgery were independent influencing factors for intraoperative hypothermia during laparoscopic surgery ($P < 0.05$). Calibration curve analysis showed good consistency between the predicted occurrence of intraoperative hypothermia and the actual occurrence ($P > 0.05$). The predictive model had AUCs of 0.850 and 0.829 for the training and validation sets, respectively.

CONCLUSION
Machine learning effectively predicted intraoperative hypothermia in polytrauma patients undergoing laparoscopic surgery, which improved surgical safety and patient recovery.

Key Words: Polytrauma; Laparoscopic surgery; Hypothermia; Related factor; Risk prediction

Core Tip: Intraoperative hypothermia is a significant concern during laparoscopic surgery in patients with multiple trauma. This study investigated the value of a machine learning model in predicting hypothermia in this patient population. The results showed that machine learning effectively predicted intraoperative hypothermia, providing a valuable tool to improve surgical safety and patient recovery. Age, baseline temperature, intraoperative temperature, duration of anesthesia, and duration of surgery were identified as independent factors influencing hypothermia. The predictive model had good accuracy and consistency in both the training and validation sets.

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INTRODUCTION

Polytrauma refers to a condition where a patient suffers multiple injuries simultaneously, which can lead to severe illness, difficulty in treatment, and high surgical risks[1]. Laparoscopic surgery has become an important means of treating patients with polytrauma. However, laparoscopic surgery poses significant risks for such patients. Intraoperative hypothermia often occurs in patients with polytrauma, which can pose a significant risk to the patient's surgical safety and postoperative recovery[2]. Hypothermia is defined as a body temperature that falls below the normal range of 36.5 °C to 37.5 °C in adults. A temperature below that range is considered hypothermic. Intraoperative hypothermia refers to a situation where a patient's body temperature drops below normal levels during surgery. Although intraoperative hypothermia is not life threatening, it increases the risk of complications. According to research, intraoperative hypothermia can lead to a series of adverse consequences such as postoperative infection, delayed wound healing, prolonged recovery time, and even death[3,4]. The incidence of intraoperative hypothermia in patients with polytrauma is more than 70%[5], and it increases gradually with the increase in surgical time. Therefore, how to effectively prevent intraoperative hypothermia in patients with polytrauma during laparoscopic surgery has become an urgent problem to be solved. Machine learning models are increasingly used in the field of medicine. Through machine learning models, large amounts of medical data can be analyzed and processed to provide accurate predictions and diagnostic results for clinical practitioners. Therefore, this study aimed to use machine learning models to predict intraoperative hypothermia in polytrauma patients undergoing laparoscopic surgery and to explore its benefits

MATERIALS AND METHODS

Subject selection

This retrospective study analyzed the clinical data of 220 patients with multiple injuries who were admitted to our hospital between June 2018 and December 2023. Of these, 154 were allocated to a training set and 66 to a validation set in a 7:3 ratio. In the training set, 53 cases experienced intraoperative hypothermia and 101 did not.

Inclusion criteria

Patients who were 18-80 years of age who underwent elective surgery under general anesthesia and had clear consciousness and the ability to communicate normally were included.

Exclusion criteria

Patients younger than 18 or older than 80 years of age; with severe cardiovascular, liver, kidney, and respiratory system disease; severe bleeding tendency; liver and kidney dysfunction, abnormal routine blood indicators; abdominal tumors or other malignant disease; preoperative infection or other preoperative complications; not able to communicate normally, with unclear consciousness, or cognitive impairment were excluded.

Methods

Study variables: Both predictive and outcome variables were included in the analysis: (1) The predictive variables were patient demographic and clinical data: sex, age, baseline temperature, body mass index (BMI), diabetes, hypertension, smoking history, alcohol consumption, intraoperative temperature, American society of anesthesiologists classification, anesthesia method, anesthesia duration, operation duration, intraoperative infusion of fluids, crystalloid infusion, colloid infusion, pneumoperitoneum flow rate, intraoperative blood loss, hemoglobin, platelet count, blood glucose, alanine aminotransferase, and aspartate aminotransferase; and (2) The outcome variable was hypothermia, and the core temperature was measured from the beginning of anesthesia until the end of surgery by an anesthesia monitor[6]. After the inducing general anesthesia, the temperature-sensitive probe of the monitor was placed in the patient's nasopharynx with a depth of the distance from the nostril to the mandibular angle on same side. The nasopharyngeal temperature was recorded every 15 min after the start of anesthesia, at the start of surgery, and until the end of surgery. The operating room temperature was maintained at 22-24 °C, and a patient temperature of < 36 °C was the diagnosis standard for intraoperative hypothermia.

Data collection methods: Screening medical records, examination reports, imaging data, and other relevant patient information using a combination of paper and electronic records ensured the completeness and accuracy of the patient information that was collected. During collection, attention was paid to protecting patient privacy and complying with legal regulations and medical ethics norms. After surgery, completed survey forms were given to a dedicated person for safekeeping, and 10% of the patient data was randomly selected for verification.

Supplementing missing data: For datasets with missing information, modeling and fitting was done to fill in missing values to ensure the completeness and accuracy of the dataset. By learning the correlation between the data before and after the model learning, the missing data values were predicted and added.

Building machine learning models: The included data were randomly sampled in a 7:3 ratio, with 70% entering the training set and 30% entering the validation set. Patients in the training set were further divided into a hypothermia group and a non-hypothermia depending on whether the they had developed hypothermia during surgery. The training set queue obtained the optimal hyperparameters through 100 iterations of fivefold cross-validation. The optimal training mode was obtained by combining all training sets, which was then brought into the corresponding validation group for verification to evaluate the model's fitting and generalization ability. The validation set selected a logistic regression classifier to construct a prediction model and used the area under the curve (AUC) to evaluate the model's discrimination. A large AUC indicated good discrimination ability of the prediction model. The model performance was evaluated by the AUC, and sensitivity, specificity, accuracy, and recall rates. The prediction model was visualized by a nomogram, and the scores of the predictive variables in the model were added together to find the corresponding point on the total score scale and a line was drawn vertically downward. The value on the corresponding probability scale was the probability of an individual experiencing an outcome event. The model's calibration was evaluated using calibration curves and the Hosmer–Lemeshow χ^2 test, which reflects the consistency between the predicted risk of intraoperative hypothermia and the actual risk in different risk-stratification patients.

Statistical analysis

The collected data were analyzed using R software (4.3.1). Normally distributed metric data were reported as means ± SD and compared by *t*-tests. Counting data were reported as numbers and percentage (%) and compared by χ^2 tests. *P* values < 0.05 indicated a significant difference. The predictive model was constructed using logistic regression, and the Hosmer–Lemeshow test was used to verify the model's goodness of fit, with a large *P* value indicating a good fit. The model's predictive ability was indicated by the AUC of the receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, and accuracy were used to verify the model's actual application efficiency.

RESULTS

Comparison of clinical data between the training set and validation set

We found no statistically significant differences of the clinical data in the training and validation sets ($P > 0.05$) as shown in Table 1).

Table 1 Comparison of clinical data

Parameter	Training (*n* = 154)	Validation (*n* = 66)	Statistical value	*P* value
Sex			$\chi^2 = 0.383$	0.536
Male	84 (54.55)	33 (50.00)		
Female	70 (45.45)	33 (50.00)		
Age in years	54.34 ± 11.58	55.87 ± 10.79	$t = 0.916$	0.361
Basal body temperature in °C	34.05 ± 0.22	34.01 ± 0.29	$t = 1.119$	0.264
BMI in kg/m^2	23.27 ± 2.82	23.65 ± 2.75	$t = 0.923$	0.357
Diabetes			$\chi^2 = 2.013$	0.156
Yes	19 (12.34)	13 (19.70)		
No	135 (87.66)	53 (80.30)		
Hypertension			$\chi^2 = 2.685$	0.101
Yes	31 (20.13)	20 (30.30)		
No	123 (79.87)	46 (69.70)		
Smoking			$\chi^2 = 2.013$	0.156
Yes	19 (12.34)	13 (19.70)		
No	135 (87.66)	53 (80.30)		
Drinking			$\chi^2 = 2.127$	0.145
Yes	15 (9.74)	11 (16.67)		
No	139 (90.26)	55 (83.33)		
Operating room temperature in °C	21.65 ± 4.16	21.52 ± 4.12	$t = 0.213$	0.832
ASA			$\chi^2 = 5.034$	0.169
I	16 (10.39)	10 (15.15)		
II	116 (75.32)	41 (62.12)		
III	21 (13.64)	13 (19.70)		
IV	1 (0.65)	2 (3.03)		
Mode of anesthesia			$\chi^2 = 0.542$	0.462
General anesthesia	71 (46.10)	34 (51.52)		
General anesthesia joint board anesthesia	83 (53.90)	32 (48.48)		
Duration of anesthesia in min	150.48 ± 76.21	139.39 ± 75.97	$t = 0.990$	0.323
Operation duration in min	127.61 ± 78.16	124.65 ± 75.77	$t = 0.260$	0.795
Intraoperative fluid infusion in mL	1067.84 ± 616.12	1073.92 ± 610.11	$t = 0.067$	0.946
Infusion of crystal solution in mL	1050.13 ± 567.08	1041.37 ± 600.42	$t = 0.103$	0.918
Infusion of colloidal solution in mL	92.68 ± 15.22	91.15 ± 15.14	$t = 0.684$	0.495
Pneumoperitoneum flow in L/min	261.22 ± 16.13	258.09 ± 15.96	$t = 1.323$	0.187
Intraoperative blood loss in mL	98.27 ± 35.82	94.18 ± 35.61	$t = 0.777$	0.438
Hemoglobin in g/L	115.65 ± 18.15	113.74 ± 17.05	$t = 0.728$	0.467
Platelet as × 10^9/L	180.88 ± 56.32	176.87 ± 56.76	$t = 0.483$	0.630
Glu in mmol/L	4.15 ± 0.87	4.25 ± 0.86	$t = 0.784$	0.434
ALT in U/L	25.58 ± 10.19	27.02 ± 10.12	$t = 0.962$	0.337
AST in U/L	20.27 ± 8.82	19.18 ± 8.75	$t = 0.842$	0.401

Data are mean ± standard deviation or *n* (%). ALT: Alanine aminotransferase; ASA: American society of anesthesiologists; AST: Aspartate

aminotransferase; BMI: Body mass index; Glu: Glucose.

Comparison of clinical data in the hypothermia and non-hypothermia groups of the training set

Statistically significant differences ($P < 0.05$) of sex, age, baseline temperature, intraoperative temperature, anesthesia duration, operation duration, intraoperative infusion of fluids, crystalloid infusion, colloid infusion, and pneumoperitoneum flow rate were observed between the hypothermia group and the non-hypothermia group. Differences were observed in other characteristics were not significant ($P > 0.05$), as shown in Table 2.

Logistic regression analysis

Assignment of the independent variables and the dependent variable is shown in Table 3. The results of logistic regression analysis indicated that age, baseline temperature, intraoperative temperature, anesthesia duration, and operation duration were independent influencing factors for intraoperative hypothermia during laparoscopic surgery ($P < 0.05$), as shown in Table 4.

Model construction and evaluation

A predictive model was established using the logistic regression analysis results. Calibration curve analysis demonstrated good consistency between the predicted and actual occurrence of intraoperative hypothermia ($P > 0.05$), as shown in Figure 1. The ROC curve analysis results indicated that the model had AUC values of 0.850 and 0.829 for predicting the occurrence of hypothermia in the training and validation set patients, respectively, as shown in Table 5 and Figures 2 and 3.

DISCUSSION

Currently, the hazards of intraoperative hypothermia are recognized by most medical staff, and the benefits of perioperative thermal insulation are recognized and recommended by many international guidelines. Relevant research in China has also begun to focus on its importance[7]. Laparoscopic techniques have become the preferred approach for most surgical procedures, yet there is a relative lack of research and data on intraoperative hypothermia in laparoscopic surgery patients. This study found that age, baseline temperature, intraoperative temperature, anesthesia duration, and operation duration were independent influencing factors for intraoperative hypothermia during laparoscopic surgery ($P < 0.05$).

Age is an important factor influencing the risk of intraoperative hypothermia in patients with multiple trauma undergoing laparoscopic surgery. With increasing age, the body's tolerance decreases, and its self-regulation functions are impaired, leading to an increased risk of intraoperative hypothermia in patients with multiple trauma. As age increases, the basal metabolic rate decreases, particularly due to an increase in fat tissue mass and a decrease in muscle tissue mass, which reduces the ability to produce heat and maintain body temperature[8]. Increasing age can also lead to a decline in temperature regulation, narrowing of the range of temperature regulation, delay of the response to change in external temperature and increase of the risk of intraoperative hypothermia[9]. Furthermore, as age increases, sympathetic nervous regulation decreases and the ability to withstand cold is reduced, resulting in weakened vascular constriction, reduced heat loss during surgery, and increased risk of intraoperative hypothermia[10].

During laparoscopic surgery, the use of surgical trauma and anesthesia drugs may further reduce heat generation. Therefore, patients with multiple trauma and low baseline temperatures are highly likely to experience insufficient heat and increased heat loss during laparoscopic surgery, thereby increasing the risk of intraoperative hypothermia[11]. Furthermore, baseline temperature may reflect the body's temperature regulation function. Body temperature is regulated by multiple physiological systems, including the central nervous system, sympathetic nervous system, and skin vascular system[12]. Patients with multiple trauma and low baseline temperatures may have abnormal or impaired temperature regulation because of weakened sympathetic nervous system activity and reduced skin blood flow that can lead to reduced heat loss during surgery and result in an increased risk of intraoperative hypothermia[13].

Regarding intraoperative temperature, the body is constantly exchanging heat with the external environment. Body temperature is closely related to environmental temperature, and heat is lost to the surrounding environment by radiation, convection, conduction, and evaporation. If more heat is lost than is generated, body temperature decreases. A low temperature can cause a decrease in body temperature, vascular constriction, and the metabolic rate of various organs. Factors affecting the metabolic rate of organs include an increase in cell membrane osmotic pressure (due to temperature reduction), which limits the exchange of substances inside and outside the cell, and reduced adenosine triphosphate (ATP) synthesis. As the metabolism is a thermodynamic process, so the energy of synthesizing ATP by the body at low temperatures decreases[14]; and enzyme catalytic activity is inhibited, which reduces the rate of chemical reactions. Thermoregulation is mainly controlled by the nervous and endocrine systems, including mechanisms such as vasodilation and constriction, sweating, and skin-surface heat loss[15]. At low temperatures, responses like shivering, capillary constriction, decreased blood flow, and increased metabolic rate occur, but cannot be maintained for a long time. The result is a decrease in body temperature[16]. One of the common side effects of anesthesia drugs is inhibition of the thermoregulation center and loop, resulting in a decrease in body temperature. At the same time, anesthesia drugs can increase muscle relaxation and slow respiration, thereby reducing the flow of deoxygenated blood and lowering the body's metabolic rate[17].

Table 2 Comparison of clinical data of patients with and without hypothermia in the training set group

Item	Hypothermia, *n* = 53	Non-hypothermia, *n* = 101	Statistical value	*P* value
Sex			χ^2 = 9.210	0.002
Male	20 (37.74)	64 (63.37)		
Female	33 (62.26)	37 (36.63)		
Age in years	61.11 ± 12.15	57.23 ± 8.71	*t* = 2.282	0.024
Basal body temperature in °C	36.15 ± 0.28	36.74 ± 0.28	*t* = 12.423	< 0.001
BMI in kg/m^2	23.73 ± 2.71	23.75 ± 3.25	*t* = 0.038	0.970
Diabetes			χ^2 = 1.715	0.190
Yes	4 (7.55)	15 (14.85)		
No	49 (92.45)	86 (85.15)		
Hypertension			χ^2 = 0.498	0.480
Yes	9 (16.98)	22 (21.78)		
No	44 (83.02)	79 (78.22)		
Smoking			χ^2 = 0.077	0.781
Yes	6 (11.32)	13 (12.87)		
No	47 (88.68)	88 (87.13)		
Drinking			χ^2 = 0.442	0.506
Yes	4 (7.55)	11 (10.89)		
No	49 (92.45)	90 (89.11)		
Operating room temperature in °C	21.12 ± 4.05	22.84 ± 5.02	*t* = 2.153	0.033
ASA			χ^2 = 4.325	0.228
I	3 (5.66)	13 (12.87)		
II	43 (81.13)	73 (72.28)		
III	6 (11.32)	15 (14.85)		
IV	1 (1.89)	0		
Mode of anesthesia			χ^2 = 0.238	0.625
General anesthesia	23 (43.40)	48 (47.52)		
General anesthesia joint board anesthesia	30 (56.60)	53 (52.48)		
Duration of anesthesia in min	162.52 ± 75.16	118.63 ± 58.35	*t* = 4.006	< 0.001
Operation duration in min	141.27 ± 75.11	99.21 ± 56.22	*t* = 3.916	< 0.001
Intraoperative fluid infusion in mL	1157.12 ± 615.51	793.15 ± 422.17	*t* = 4.319	< 0.001
Infusion of crystal solution in mL	1046.01 ± 560.12	769.34 ± 389.25	*t* = 3.585	0.001
Infusion of colloidal solution in mL	103.41 ± 15.06	27.79 ± 7.15	*t* = 42.274	< 0.001
Pneumoperitoneum flow in L/min	270.51 ± 17.21	187.29 ± 11.19	*t* = 36.200	< 0.001
Intraoperative blood loss in mL	118.33 ± 33.95	112.79 ± 35.31	*t* = 0.937	0.350
Hemoglobin in g/L	134.98 ± 20.85	136.58 ± 19.69	*t* = 0.469	0.639
Platelet as × 10^9/	208.76 ± 62.16	211.41 ± 59.52	*t* = 0.259	0.796
Glu in mmol/L	5.14 ± 0.95	5.21 ± 1.06	*t* = 0.403	0.687
ALT in U/L	26.89 ± 10.41	25.79 ± 10.68	*t* = 0.612	0.541
AST in U/L	21.27 ± 9.12	20.39 ± 8.97	*t* = 0.575	0.566

Data are mean ± standard deviation or *n* (%). ALT: Alanine aminotransferase; ASA: American society of anesthesiologists; AST: Aspartate

aminotransferase; BMI: Body mass index; Glu: Glucose.

Table 3 Variable assignment

Variable	Factor	Assignment
Y	Hypothermia	1 = hypothermia; 0 = non-hypothermia
X1	Age	Continuous variable, original value input
X2	Basal body temperature	Continuous variable, original value input
X3	Operating room temperature	Continuous variable, original value input
X4	Duration of anesthesia	Continuous variable, original value input
X5	Operation duration	Continuous variable, original value input
X6	Intraoperative fluid infusion	Continuous variable, original value input
X7	Infusion of crystal solution	Continuous variable, original value input
X8	Infusion of colloidal solution	Continuous variable, original value input
X9	Pneumoperitoneum flow	Continuous variable, original value input
X10	Sex	0 = Male; 1 = Female

Table 4 Multivariate logistic regression analysis

Risk factor	β	SE	Wald χ^2	*P* value	OR	95%CI
Age	0.056	0.017	11.434	0.001	1.058	1.024-1.093
Basal body temperature	−1.211	0.365	11.157	0.001	0.286	0.231-0.976
Operating room temperature	−0.066	0.041	2.688	0.101	0.936	0.864-1.013
Duration of anesthesia	−0.008	0.003	8.458	0.004	0.992	0.986-0.997
Operation duration	0.011	0.003	12.787	< 0.001	1.011	1.005-1.018

95%CI: 95% Confidence interval; OR: Odds ratio; SE: Standard error.

Table 5 Nomogram model for predicting the occurrence of hypothermia during laparoscopic surgery

Index	AUC	SEN, %	SPE, %	95%CI	*P* value
Training	0.850	94.69	91.47	0.909-0.962	< 0.001
Validation	0.829	95.38	90.53	0.850-0.988	< 0.001

95%CI: 95% Confidence interval; AUC: Area under the curve; SEN: Sensitivity; SPE: Specificity.

Regarding anesthesia duration, a long duration can damage the temperature regulation center, thereby affecting the ability to control temperature. Anesthesia drugs can inhibit the activity of the temperature regulation center and reduce the metabolic rate, leading to a decrease in body temperature. During long surgical procedures, the body-heat conduction is restricted[18]. During surgery, the patient is exposed on the surgical table, which is a relatively cold surface that causes increased heat loss from the body surface[19]. In addition, the surgical procedure may expose internal organs, which can lead to increased heat loss.

Regarding operation duration, patients with multiple trauma undergoing long operations are in a state of dormancy due to the need for general anesthesia, and their metabolic rate slows, leading to a decrease in body temperature. Anesthesia drugs can inhibit the metabolic activity of the central nervous system, thereby reducing energy consumption, slowing the body's heat production and ability to preserve heat, and thus lower body temperature[20]. In laparoscopic surgery, carbon dioxide is used to inflate the abdomen to expand the surgical space. Given the ability of carbon dioxide to absorb heat, it absorbs surrounding heat into the abdomen and affects the gas exchange of the alveoli, leading to an increase in the concentration of carbon dioxide in the body[21]. These factors can cause a decrease in body temperature. Local tissue damage and bleeding during surgery can also increase energy consumption, leading to a decrease in body

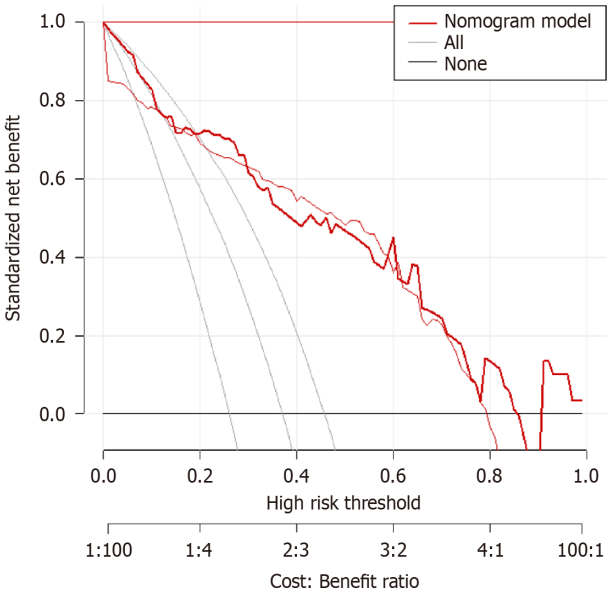

Figure 1 Calibration curve.

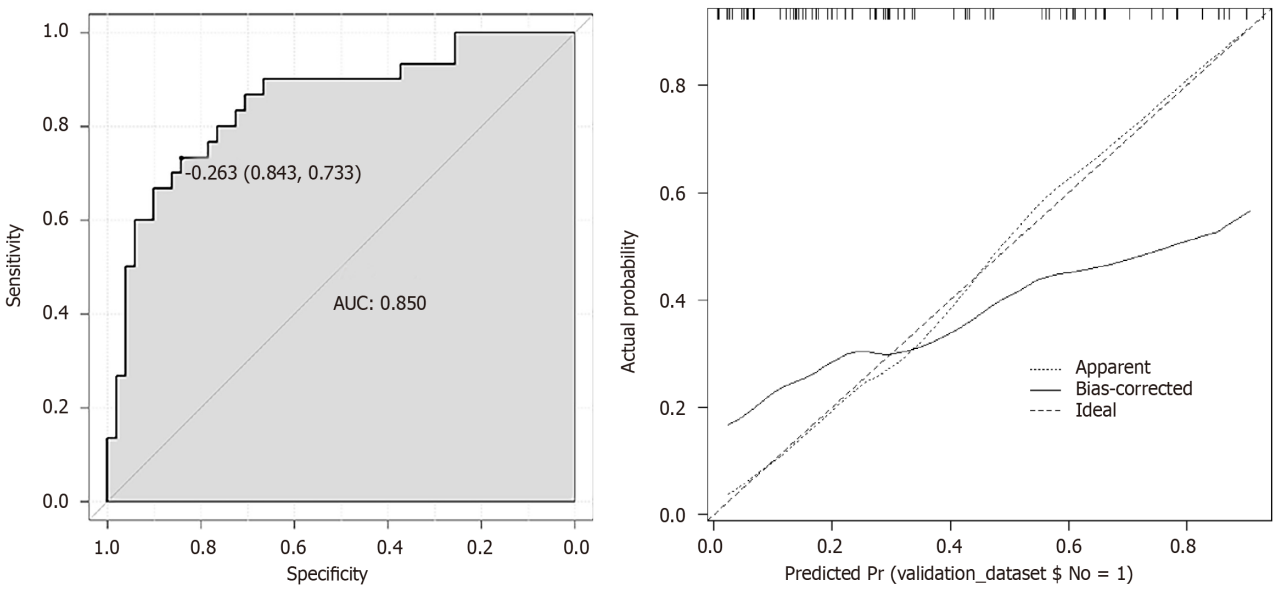

Figure 2 Predictive value and calibration curve of intraoperative hypothermia in the training set. AUC: Area under the curve; Pr: Probability.

temperature. Research has shown[22] that the incidence of intraoperative hypothermia increases significantly when the operation time exceeds 2 h, which is consistent with the results of this study.

BMI is an important factor influencing intraoperative hypothermia during laparoscopic surgery[23]. Previous studies demonstrated[24] that patients with high BMIs have reduced surface heat loss owing to the protective effect of fat, which results in a small difference between core temperature and surface temperature and a low incidence of hypothermia. However, this study did not find BMI was a factor that influenced the occurrence of hypothermia during laparoscopic surgery.

Based on the logistic regression analysis results, age, baseline temperature, intraoperative temperature, anesthesia duration, and operation duration were included in the predictive model. Calibration curve analysis demonstrated good consistency between the predicted and actual occurrence of intraoperative hypothermia ($P > 0.05$). ROC curve analysis results showed that the model had AUC values of 0.850 and 0.829, respectively, for predicting the occurrence of hypothermia in the training set and validation set patients. The above results indicate that the model had good predictive ability and accuracy.

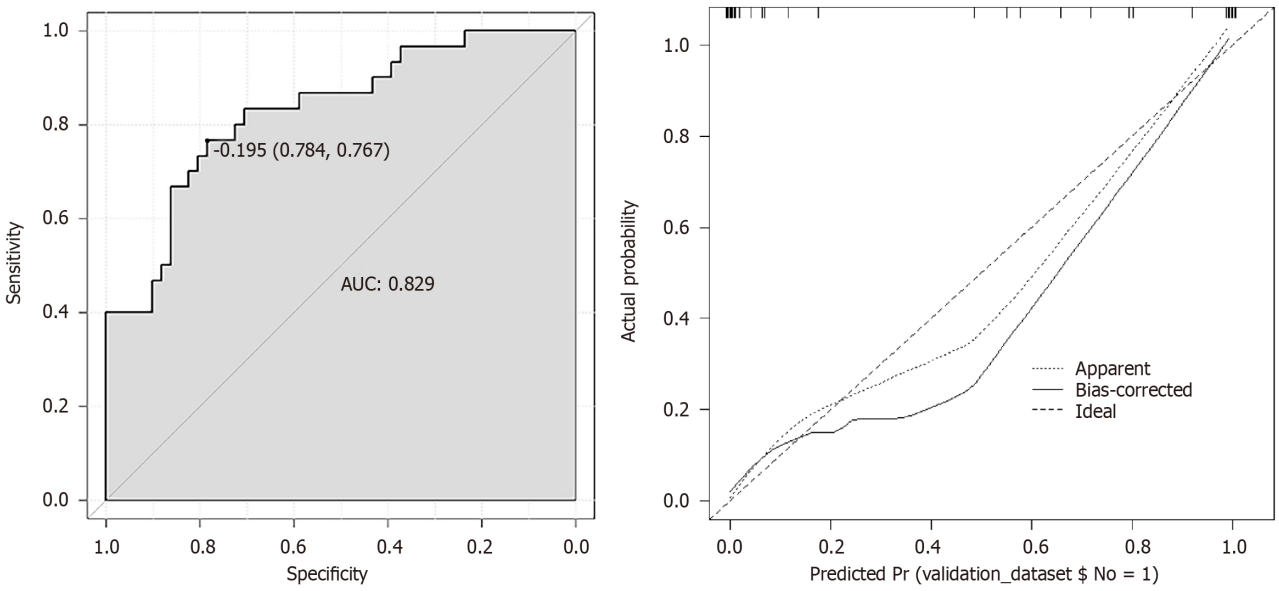

Figure 3 Verification of the predictive value of intraoperative hypothermia and the calibration curve. AUC: Area under the curve; Pr: Probability.

CONCLUSION

A predictive model of the risk of intraoperative hypothermia in laparoscopic surgery patients was developed using data from multiple dimensions, including demographic data, surgery, anesthesia, and the environment, using a random forest algorithm. The random forest algorithm has significant advantages in predicting the risk of intraoperative hypothermia in laparoscopic surgery patients. It can identify important influencing factors of intraoperative hypothermia from a complex group of multiple factors by comprehensive evaluation. The result is of great significance for clinical and medical staff to identify high-risk patients in a timely manner and adopt effective intervention measures. However, the study had limitations. It included only laparoscopic surgery patients from our hospital, which may have introduced information bias and patient selection bias in the data collection process. Moreover, the study sample was relatively small. In future studies, we will collaborate with multiple centers, increase the sample size, include additional variables, and continuously optimize this predictive model of the risk of intraoperative hypothermia in laparoscopic surgery patients.

FOOTNOTES

Author contributions: Zhu K, Zhang ZX and Zhang M designed the experiments and conducted clinical data collection, performed postoperative follow-up and recorded the data, conducted the collation and statistical analysis, and wrote the original manuscript and revised the paper; All authors read and approved the final manuscript. Zhu K and Zhang ZX are co-first authors and contributed equally to this work, including design of the study, acquiring and analyzing data from experiments, and writing of the manuscript.

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ORIGINAL ARTICLE

Clinical Trials Study

Effectiveness of the A3 robot on lower extremity motor function in stroke patients: A prospective, randomized controlled trial

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Abstract

BACKGROUND

The results of existing lower extremity robotics studies are conflicting, and few relevant clinical trials have examined short-term efficacy. In addition, most of the outcome indicators in existing studies are scales, which are not objective enough. We used the combination of objective instrument measurement and scale to explore the short-term efficacy of the lower limb A3 robot, to provide a clinical reference.

AIM

To investigate the improvement of lower limb walking ability and balance in stroke treated by A3 lower limb robot.

METHODS

Sixty stroke patients were recruited prospectively in a hospital and randomized into the A3 group and the control group. They received 30 min of A3 robotics training and 30 min of floor walking training in addition to 30 min of regular rehabilitation training. The training was performed five times a week, once a day, for 2 wk. The *t*-test or non-parametric test was used to compare the three-dimensional gait parameters and balance between the two groups before and after treatment.

RESULTS

The scores of basic activities of daily living, Stroke-Specific Quality of Life Scale, FM balance meter, Fugl-Meyer Assessment scores, Rivermead Mobility Index, Stride speed, Stride length, and Time Up and Go test in the two groups were significantly better than before treatment (19.29 ± 12.15 *vs* 3.52 ± 4.34; 22.57 ± 17.99 *vs* 4.07 ± 2.51; 1.21 ± 0.83 *vs* 0.18 ± 0.40; 3.50 ± 3.80 *vs* 0.96 ± 2.08; 2.07 ± 1.21 *vs* 0.41 ± 0.57; 0.89 ± 0.63 *vs* 0.11 ± 0.32; 12.38 ± 9.00 *vs* 2.80 ± 3.43; 18.84 ± 11.24 *vs* 3.80 ± 10.83; 45.12 ± 69.41 *vs* 8.41 ± 10.20; 29.45 ± 16.62 *vs* 8.68 ± 10.74; $P < 0.05$). All outcome indicators were significantly better in the A3 group than in the control group, except the area of the balance parameter.

CONCLUSION

For the short-term treatment of patients with subacute stroke, the addition of A3 robotic walking training to conventional physiotherapy appears to be more effective than the addition of ground-based walking training.

Key Words: Stroke; Robotics; Gait; Robot-assisted gait training; Neurological rehabilitation; Walking training

Core Tip: In this study, two groups of stroke patients underwent 2 wk of A3 lower extremity robotics and ground walking training, respectively, and gait spatiotemporal and balance parameters were recorded before and after the 2-wk intervention, which were compared by statistical analysis. It was finally concluded that for the short-term treatment of patients with subacute stroke, the addition of A3 robotic walking training to conventional physiotherapy appears to be more effective than the addition of ground-based walking training.

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INTRODUCTION

Stroke can lead to permanent disability and even death[1]. In many cases following a stroke, mobility, balance, and walking are affected[2], The majority of stroke survivors have initial mobility deficits, and 6 mo after stroke, more than 30% of survivors still cannot walk independently[3] and impaired gait still severely limits daily life. Gait pattern abnormalities associated with stroke are often characterized by altered hip, knee, and ankle kinematics[4], and stroke patients walk asymmetrically and with reduced gait speed[5]. One of the main goals of stroke rehabilitation is to regain gait function[6], and therapists spend a considerable amount of time and effort on it[7].

Lower limb robot is a new treatment method to promote the recovery of stroke patients. It has the advantages of repetition, specificity, and quantitative evaluation[8,9]. Studies have shown that patients with subacute stroke who received lower limb robots in combination with conventional treatment showed greater improvement in functional gait than those who received conventional treatment alone[10-12]. But other studies have found no difference in outcomes between robotic therapy and traditional therapy[13-15] and the issue remains controversial and unresolved. Therefore, the application of gait robots to the field of stroke needs more research to expand some obscure and controversial areas. In addition, most of the previous clinical trials of lower limb robots used scales such as the Fugl-Meyer Assessment scale, Berg Balance Scale scores, and River mead Mobility Index (RMI) to evaluate the efficacy[12], which is subjective to a certain extent. Three-dimensional gait analysis has the advantages of objective data, quantitative data, and high credibility[16].

Based on the above background, a clinical trial was conducted to verify the effectiveness of 2-wk A3 lower limb robot-assisted gait training on patients with subacute stroke, and three-dimensional gait spatiotemporal parameters were used as evaluation indexes. We propose a basic hypothesis: in the short term, patients with subacute stroke who added A3 robotic walking training to conventional physical therapy showed significant gait and balance improvements in spatial-temporal parameters and balance function that may be superior to conventional ground-based walking training.

MATERIALS AND METHODS

Study design

This study was a single-center, single-blind, and prospective randomized controlled trial. The clinical trial was approved by the Ethics Committee of Yuebei People's Hospital (KY-2021-327; Shaoguan, China). Written informed consent was provided by all participants and the procedures were carried out following the Helsinki Declaration. The program was registered online in the Chinese Clinical Trial Registry (Registration No. ChiCTR2100052767).

Before the trial, eligible participants were randomly assigned to two groups according to a random number generated by Excel software. The random numbers were written on a small card and placed in an opaque envelope. An investigator determined the eligibility of participants for inclusion, but he was not involved in the allocation and was not aware of subsequent grouping (hidden assignment). After the patient grouping was confirmed by two therapist interveners, the grouping sheet was kept in a sealed opaque envelope until the end of the trial. At the end of the trial, no errors were found after we uncovered and checked the allocation.

Participants

Subjects were selected according to the following inclusion criteria: (1) Enrolled patients had a first stroke diagnosed by computerized tomography or magnetic resonance imaging (MRI); (2) All patients have unilateral limb motor dysfunction, and the patient can complete a 10 m walk alone or with the assistance of an assistive device; (3) The patient's condition, including vital signs, remained stable; (4) Aged 25 years to 80 years; (5) Lower extremity Brunnstrom stage III (inclusive) or higher, lower extremity modified Ashworth grading muscle tone below grade II; (6) Patients can cooperate with researchers in various examinations and rehabilitation training; and (7) The patient himself and his family members provided written informed consent.

Exclusion criteria are as follows: (1) Patients with other nervous system or bone and joint diseases that may affect the function of the lower extremities, such as arthritis, lower extremity joint contractures, deformities or other peripheral nervous system lesions, pain conditions; (2) Pregnant and lactating patients; (3) Patients with severe cardiopulmonary insufficiencies, such as heart failure, unstable angina, *etc*, or implanted pacemakers; (4) Patients with severe osteoporosis, malignant tumor of bone and joint; and (5) Patients with severe sensory impairment.

Interventions

Intervention group (A3 group). The intervention group received 30 min of routine lower extremity training and robot-assisted gait assessment and training system A3 (RAGATS-A3, NX, Shanghai, China) supplemented with conventional rehabilitation training. RAGATS-A3 is a rehabilitation robot device, as presented in Figure 1, which assists patients with lower limb dysfunction to conduct gait correction and motor relearning training. It includes exoskeleton mechanical legs, dynamic and static weight reduction system, buffer runway, and situational feedback display screen, *etc.* Perhaps due to its high price, few clinical trials have investigated the robot's short-term effectiveness on lower limb gait in patients with subacute stroke. Based on the principle of neural plasticity, walking function can be restored through continuous training. The robot consists of an exoskeleton mechanical leg, running table, weight loss system, situational feedback game, and gait analysis system. The operator can monitor the patient's movement in real-time through sensors mounted on the hip, knee, and ankle, thus accurately controlling the range and walking speed of the hip, knee, and ankle joints. Combined with virtual reality technology and dynamic or static weight loss systems, the robot can provide high-intensity, repeatable, task-oriented comprehensive walking training. Before the training, part of the patient's body weight was supported by a suspension weight loss system, after which both lower limbs were attached to the mechanical leg of the exoskeleton, and both ankle joints were secured in a neutral position using foot straps at last. We set the training mode to automatic, the weight loss support level to 50%, the speed of the exercise plate to 1.0-1.2km/h, and the guiding force to 100%. Later, as the patient's movement improved, the weight loss support and guiding force were gradually reduced (minimum to 0%) according to the tolerance of each patient[17-19]. Excluding the time spent installing and adjusting the equipment, the effective training duration was 30 min.

Control group. Patients in the control group received ground walking training under the supervision or with little assistance from the therapist. The primary role of the therapist is to prevent the patient from falling and to give verbal instructions when necessary. Each treatment lasted for 30 min, once a day, five times/wk.

In addition, prior to each intervention in the clinical trial, all patients will receive 30 min of conventional physical training based on traditional neurodevelopmental techniques including sitting and standing balance training, functional transfer training, affected limb weight training, foot following training, stride training, and dynamic balance training. This training aims to improve the patient's gait, posture, and stability during walking, correct the muscular lines of the body during walking, and assist the patient to re-establish a normal walking pattern. Conventional physical training for all patients was performed by the same experienced senior rehabilitation therapist who did not participate in the entire assessment process. Each treatment lasted for 30 min, once a day, 5 times/wk. Briefly, patients in the A3 group received 30 min of conventional physical training and 30 min of A3 training, whereas the control group received 30 min of conventional physical training and 30 min of conventional ground walking. All participants received a 60-min training intervention per day for 2 wk (5 times/wk, a total of 10 times). In addition, other treatments, including medication, were the same for two groups of patients. We chose a 2-wk treatment period because Chinese and local health insurance policies stipulate that stroke patients can be hospitalized for up to 2 wk when using health insurance to reimburse hospitalization costs. Without health insurance coverage, the burden of healthcare for Chinese residents would be very heavy. This also poses a huge challenge for us as healthcare professionals, and we hope to find ways to maximize the benefits for our patients in the short term.

Outcomes

The primary results were the three-dimensional gait spatiotemporal parameters monitored by the machine (Gait Watch; Zhang He Zhi Neng, Guangzhou, China) (Figure 2) in real time. Specific operation (additional information regarding the manufacturer's website: http://www.ezhanghe.com/) was as follows. The motion sensors were fixed on each joint of the patient's lower limbs (Figure 2), telling the patient to walk 12 m, in the presence of medical staff and family members (no contact with the patient, let the patient walk independently) to and from two times. The machine sensors evaluate and

Figure 1 Robot-assisted gait assessment and training system A3, NX, China (Yikang Yiliao and Yuebei People's Hospital).

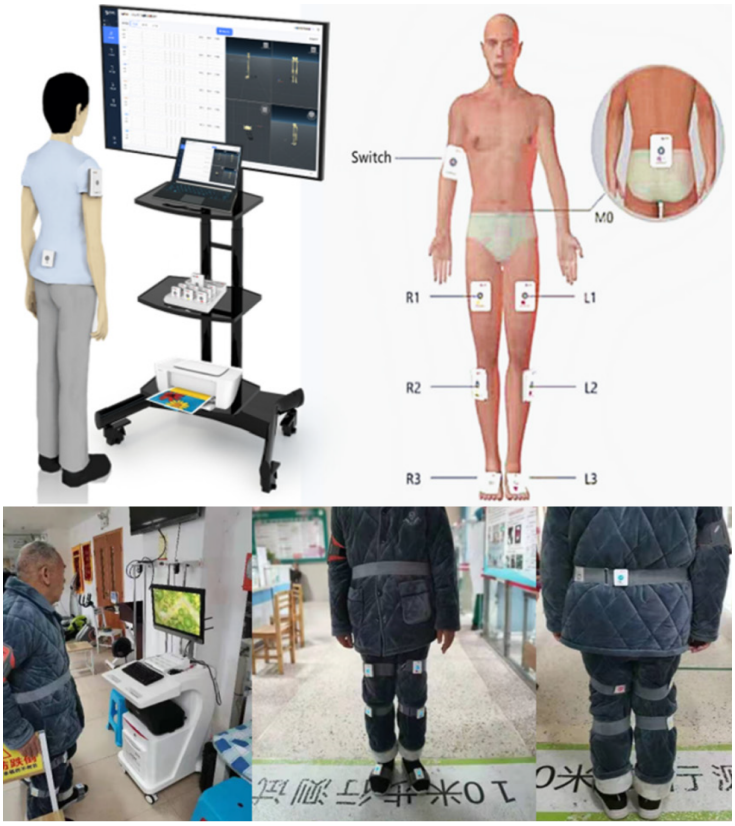

Figure 2 Gait watch, Zhang He Zhi Neng, Guangzhou, China (Gait watch and the position diagram of wearing sensor. Switch: Upper right arm; M0: Upper sacral margin; R/L1: The anterior side of the midsection of the femur; R/L2: Lower edge of the fibula head; R/L3: Behind the metatarsophalangeal joint, the second through the fourth metatarsal bones.

record detailed temporal and spatial parameters of the gait, dynamically observe the patient's gait, and provide a comprehensive picture of the progress of each joint movement during walking. Spatial parameters of the gait include stride frequency, stride length, stride speed, and other basic parameters.

Secondary assessment results were balance parameters (balancing apparatus: Union Rehab, Balance test training system: PC708; Beijing, China) (Figure 3), The balance parameters we selected included gravity center moving track length (Lng), gravity center moving track area (Area), and track length per unit area (TL index)[20], which were automatically generated by the balancing instrument. First, subjects were required to stand on the gravity-sensitive platform of the machine in a standard posture, look directly at the screen in front of them, and relax their hands. Two tests lasting 30 s

Figure 3 Union rehab PC-708 balance machine, Beijing, China.

were carried out: one with eyes open and one with eyes closed. During this process, the machine automatically measured and calculated the value of the balance parameter. Each patient was performed twice and the average score was recorded (Figure 3)[21]. TL index is the value obtained by dividing the total trajectory length of the center of gravity movement by the area of the trajectory of the center of gravity movement within a given time. This value is inversely proportional to the area and directly proportional to the Lng, which reflects the balance stability of the body and the adjustment ability of posture balance. The larger the value, the stronger the adjustment ability[20,22].

In addition, Fugl-Meyer-Assessment (FMA) scores (including aspects of balance and lower extremity) and RMI[23], Time Up and Go test (TUG)[24], and basic activities of daily living (BADL)[25], FM balance meter, Stroke-Specific Quality of Life Scale (SSQOL)[26], and Holden Walking Ability Scale(HWAS)[21] values were collected for recording. Adverse events are also recorded. The patients were evaluated at baseline and after 2 wk of treatment by a specialist evaluator who did not know the exact allocation, and each assessment was carried out more than twice and then averaged.

Statistical analysis

The data were analyzed using SPSS Statistics version 26.0. The assumption of normality of data was assessed using the Kolmogorov-Smirnov test. The χ^2 test was used to test the baseline data of the two groups, such as sex, stroke type, and other categorical data. Data are expressed as the mean ± standard deviation; otherwise, the median and interquartile range was used. The independent *t*-test was used for normally distributed data, and the Mann-Whitney *U* test was used for non-normally distributed data. Paired *t*-test was used for statistical analysis of the changes before and after treatment in the same group. $P < 0.05$ was considered statistically significant.

RESULTS

Recruiting patients

A total of 60 stroke patients who met the inclusion criteria volunteered to participate in the study between November 2021 and November 2022. They were randomly assigned to either the control group or the intervention group (A3 group). The Control group ($n = 30$) received conventional rehabilitation training while the A3 group ($n = 30$) received a combination of robot-assisted training and conventional rehabilitation therapy. Five fell off, and fifty-five were eventually included in the analysis. The screening and allocation process is shown in Figure 4.

Baseline data of patients

The A3 group included 28 patients and the control group included 27 patients. There were no significant differences in sex ratio, stroke type, the proportion of hypertension and diabetes mellitus, average age, and course of disease between the two groups ($P > 0.05$), indicating that the two groups were comparable. The baseline data of patients are shown in Table 1.

Comparison of two groups before and after intervention

The situation of patients in both groups after 2 wk of intervention can be seen in Table 2. The scores of BADL, SSQOL, FM balance meter, FMA, RMI, Stride speed, Stride length, and TUG in the two groups were significantly better than before treatment ($P < 0.05$). Although the HWAS, Stride frequency, Lng, Area, and TL index scores of the control group after 2

Table 1 Baseline data of patients

Parameter		A3 group	Control group	*P* value
Sex	Male	22	22	0.787
	Female	6	5	
Age in yr		52.14 ± 15.352	58.48 ± 17.194	0.155
Height in cm		163.21 ± 4.756	165.52 ± 7.361	0.177
Weight in kg		63.21 ± 7.733	67.48 ± 9.928	0.080
Type of stroke	Infarction	17	17	0.864
	Hemorrhage	11	10	
Paretic side	Right	12	14	0.504
	Left	16	13	
Hypertension	Yes	20	21	0.589
	No	8	6	
Diabetes	Yes	5	6	0.686
	No	23	21	
Mean time since stroke in d		49.71 ± 36.054	43.63 ± 42.164	0.567
MMSE		27.50 ± 4.308	27.19 ± 2.354	0.739
BADL		67.14 ± 15.836	71.67 ± 10.561	0.220
Brunnstrom stage		3.68 ± 0.863	3.89 ± 0.801	0.353
SSQOL		156.36 ± 23.429	154.67 ± 17.236	0.762
FM balance meter		8.54 ± 0.999	8.52 ± 0.700	0.942
FMA of lower limbs		20.07 ± 5.643	21.22 ± 5.820	0.460
RMI		8.75 ± 1.936	8.44 ± 1.281	0.495
HWAS		2.86 ± 0.756	2.81 ± 0.736	0.834
TUG in s		32.404 ± 14.726	29.643 ± 12.348	0.455
Stride frequency as step/min		76.018 ± 19.978	86.093 ± 17.100	0.050
Stride speed in cm/s		45.643 ± 19.187	53.389 ± 23.009	0.180
Stride length in cm		70.054 ± 18.921	72.426 ± 24.722	0.690
Lng		1360.61 ± 774.611	1463.70 ± 1061.382	0.682
Area		1889.64 ± 1334.954	2165.63 ± 1474.666	0.470
TL index		0.901 ± 0.361	0.941 ± 0883	0.828

Data are mean ± standard deviation. Area: Gravity center moving track area; BADL: Basic activities of daily living; FMA: Fugl-Meyer-Assessment scores; HWAS: Holden Walking Ability Scale; Lng: Gravity center moving track length; MMSE: Mini-mental state examination; RMI: Rivermead Mobility Index; SSQOL: Stroke-Specific Quality of Life Scale; TL index: Track length per unit area; TUG: Time Up and Go test.

wk were better than that of the 2 wk before, there was no statistically significant difference ($P > 0.05$). By contrast, the above indexes of A3 group were significantly better after 2 wk than before 2 wk ($P < 0.05$).

Comparison of the amount of change in clinical outcomes

We used the change from baseline to 2 wk later as the effect size to objectively compare the efficacy of the two groups, which could overcome the inconsistencies in the baseline and be more objective and accurate than the direct comparison of efficacy results after treatment. The results of the efficacy comparison between the A3 and control groups are shown in Table 3.

We could find that adding the A3 robot intervention to the control group significantly improved patients' BADL, SSQOL, FM balance meter, FMA, RMI, HWAS, and TUG scores ($P < 0.01$), and the A3 rehabilitation robot can significantly improve the temporal and spatial parameters of patients in terms of gait frequency, stride length, and gait speed ($P < 0.01$). In terms of balance, the A3 rehabilitation robot group showed significantly higher improvement in Lng and TL indices than the control group ($P < 0.05$); however, there was no significant difference in improvement in Area (P

Table 2 Comparison of two groups before and after intervention

Outcome	A3 group		Control group	
	Baseline	2 wk	Baseline	2 wk
BADL	67.14 ± 15.836	86.43 ± 10.874[a]	71.67 ± 10.561	75.19 ± 9.556[a]
SSQOL	156.36 ± 23.429	178.93 ± 23.650[a]	154.67 ± 17.236	158.74 ± 17.295[a]
FM balance meter	8.54 ± 0.999	9.75 ± 1.456[a]	8.52 ± 0.700	8.70 ± 0.542[a]
FMA (lower limbs)	20.07 ± 5.643	23.57 ± 5.473[a]	21.22 ± 5.820	22.19 ± 6.032[a]
RMI	8.75 ± 1.936	10.82 ± 1.679[a]	8.44 ± 1.281	8.85 ± 1.460[a]
HWAS	2.86 ± 0.756	3.75 ± 0.585[a]	2.81 ± 0.736	2.93 ± 0.675[b]
TUG(s)	32.404 ± 14.726	20.029 ± 7.228[a]	29.643 ± 12.348	26.842 ± 9.600[a]
Stride frequency as step/min	76.018 ± 19.978	94.857 ± 17.678[a]	86.093 ± 17.100	89.889 ± 13.480[b]
Stride speed in cm/s	45.643 ± 19.187	90.768 ± 77.937[a]	53.389 ± 23.009	61.796 ± 21.825[a]
Stride length in cm	70.054 ± 18.921	99.500 ± 26.606[a]	72.426 ± 24.722	81.111 ± 22.263[a]
Lng	1360.61 ± 774.611	925.36 ± 408.597[a]	1463.70 ± 1061.382	1397.04 ± 948.131[b]
Area	1889.64 ± 1334.954	980.96 ± 728.462[a]	2165.63 ± 1474.666	1755.59 ± 987.181[b]
TL index	0.901 ± 0.361	1.352 ± 0.665[a]	0.941 ± 0883	0.952 ± 0.499[b]

Data shown are mean ± SD, P values are from t-test and chi-square test.
[a]$P < 0.05$, comparison of the same group before and after the intervention.
[b]$P > 0.05$, comparison of the same group before and after the intervention.
Area: Gravity center moving track area; BADL: Basic activities of daily living; FMA: Fugl-Meyer-Assessment scores; HWAS: Holden Walking Ability Scale; Lng: Gravity center moving track length; RMI: Rivermead Mobility Index; SSQOL: Stroke-Specific Quality of Life Scale; TL index: Track length per unit area; TUG: Time Up and Go test.

Table 3 Comparison of the amount of change in clinical outcomes

Change	A3 group	Control group	*P* value
BADL	19.286 ± 12.150	3.518 ± 4.344	< 0.01
SSQOL	22.571 ± 7.988	4.074 ± 2.510	< 0.01
FM balance meter	1.214 ± 0.832	0.185 ± 0.396	< 0.01
FMA	3.500 ± 3.805	0.963 ± 2.084	< 0.01
RMI	2.071 ± 1.215	0.407 ± 0.572	< 0.01
HWAS	0.893 ± 0.629	0.111 ± 0.320	< 0.01
TUG	12.376 ± 8.997	2.801 ± 3.430	< 0.01
Stride frequency	18.839 ± 11.236	3.796 ± 10.829	< 0.01
Stride speed	45.125 ± 69.409	8.407 ± 10.202	0.009
Stride length	29.446 ± 16.624	8.685 ± 10.736	< 0.01
Lng	435.250 ± 570.537	66.666 ± 517.694	0.015
Area	908.678 ± 972.848	410.037 ± 1186.491	0.094
TL index	0.451 ± 0.543	0.012 ± 0.732	0.014

Data shown are mean ± SD, P values are from t-test. Area: Gravity center moving track area; BADL: Basic activities of daily living; FMA: Fugl-Meyer-Assessment scores; HWAS: Holden Walking Ability Scale; Lng: Gravity center moving track length; RMI: Rivermead Mobility Index; SSQOL: Stroke-Specific Quality of Life Scale; TL index: Track length per unit area; TUG: Time Up and Go test.

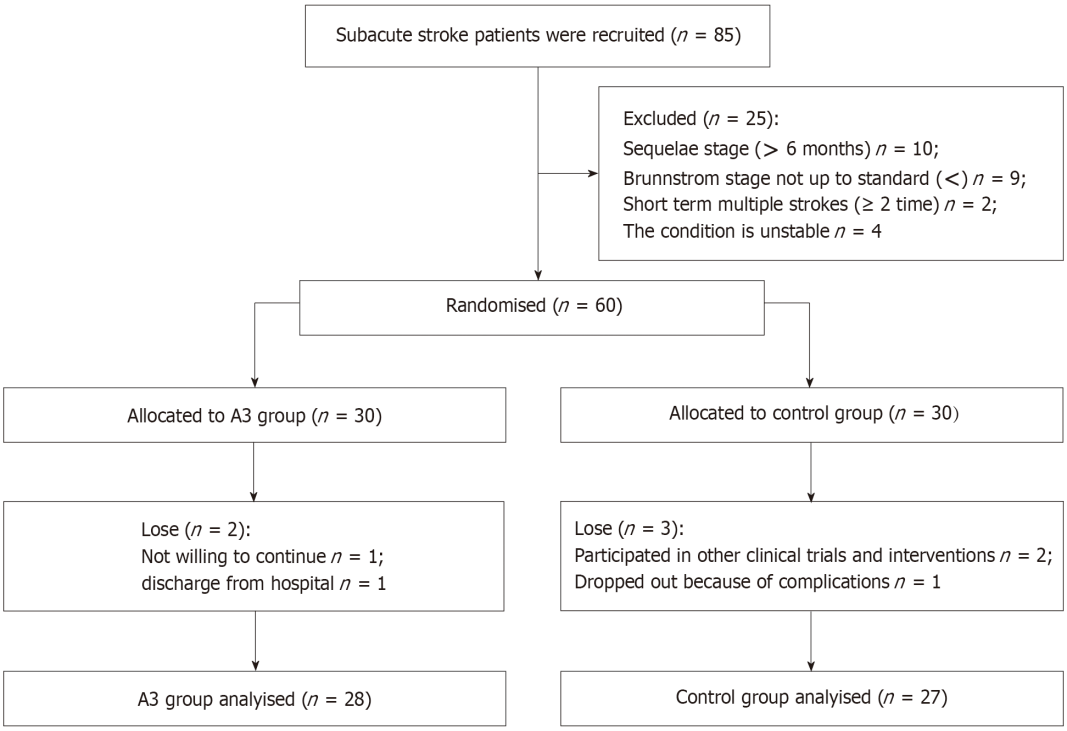

Figure 4 Recruitment allocation flow diagram of this study.

= 0.094).

Safety and adverse events

In this study, there were no serious adverse events in either group and no adverse effects in the control group. In the A3 group, 2 patients reported crotch-pulling pain during weight loss, which was reduced or disappeared after appropriate adjustment of the weight loss index and adjustment of wear, and all discomfort disappeared completely within 1 h after completion of the A3 robot.

DISCUSSION

The purpose of this randomized controlled trial was to compare the short-term therapeutic effects of the A3 gait robot combined with conventional walking training on the improvement of motor function and balance coordination in stroke patients; thus, providing medical evidence for the clinical value of this robot. Our results showed that the combined treatment improved walking function more significantly than traditional gait training in the short term. Notably, the control group showed a numerical but not statistically significant improvement in balance parameters, HWAS, and Stride frequency after 2 wk. After team discussion and analysis, we agreed that this may be related to the small sample size and the short duration of the intervention, after all, 2 wk of regular walking training showed limited improvement in patients in Brunnstrom stage III, because we included patients who were able to stand and had a walking base. At least for the indicator of stride frequency, our results are consistent with those of Yu *et al*[19] in that 2 wk of training did not change the patients' stride frequency, which could reasonably explain the clinical benefit but no statistical difference. When we used the amount of change before and after the intervention as an effect size to compare the efficacy of the two groups, all results (including quality of life, walking ability, gait parameters, motor balance function, *etc*., except Area, showed greater improvement in the A3 group than in the control group. This also suggests that a 2-wk robotic intervention can accelerate the improvement of gait and balance coordination function in the lower extremities of patients with subacute stroke. Understood from another perspective, we believe that perhaps the duration of the robotic intervention is recommended to be 2 wk or longer to see a significant improvement, because in the present trial, even with 2 wk of robotic intervention, there was still no significant difference in one of our 13 outcome indicators.

We chose to use this A3 robot from China Yikang because the product has its own characteristics. Compared to the Walkbot and Lokomat robots that are widely used today, the A3 system optimizes the training program and gait data by incorporating the normal gait curves of the Chinese population. Compared to the two foreign systems, the system analyzes results that are more suitable for the exercise patterns of the experimental population, reduces the error of the experimental results, and ensures that the patients establish the correct exercise patterns. In addition, the lower limb exoskeleton size of the A3 robot, which has been applied and improved for more than 10 years, conforms to the physical characteristics of Chinese people, and the changes in the results before and after the experiment can effectively reflect the treatment efficacy. The adjustable hip and knee offset range in the A3 system is -10°-10 degrees, with 20 adjustable steps,

which can gradually correct abnormal movement patterns during training. Not only that, the A3 robot also has a spasm detection and stopping protection function, which can satisfy all stages of walking rehabilitation in the early stage of stroke patients' rehabilitation treatment with the dynamic and static weight reduction function. Adjustable active and passive training guiding force adapts to different training progress of patients, providing challenging training and stimulating neural remodeling. And the rich gaming experience of A3 with no less than six game scenes and visual input feedback help activate new neural circuits and realize neural remodeling. Considering these reasons, we believe it is necessary to conduct this study to validate the efficacy of the A3 robot.

Our innovation is to observe whether a short-term A3 robotic intervention is effective in improving lower extremity walking and balance in patients with subacute stroke, in addition to using a combination of objective instrumental measurements and subjective scales, which is more objective and reliable. Several previous studies[27,28] have reported the effects of lower extremity robotics compared to conventional walking training in patients with subacute stroke, but more attention has been paid to the long-term effects between 1 and 2 mo or 6 mo later[29]. Considering the limited resources and time cost, it is difficult for many patients to complete the entire course of treatment, thus affecting the judgment of the therapeutic effect of this product. Therefore, our study focused on its short-term benefits. Compared with previous similar studies we developed more stringent screening inclusion criteria, focusing on patients with certain walking potential within 6 mo after the onset of disease, to most intuitively measure and compare patients' function before and after the intervention. Furthermore, the total length and total area of the walking trajectory of patients were also included in the comparison and analysis of outcome indicators, reflecting patients' dynamic balance and walking stability. Barthel Index and SSQOL scores were also analyzed and compared to more fully assess patients' functional walking ability in daily life rather than just the immediate improvement after training.

There is some basis for the hypothesis that lower extremity robots promote mechanisms of walking and balance. By altering mitochondrial dynamics, exercise training improves skeletal muscle oxidative capacity[30]. The exoskeleton part of the A3 robot wraps around the patient's lower limbs to drive walking, which enhances the patient's proprioception and leads to an easier somatosensory sensation, which is also one of the reasons for the improved balance function[27]. The A3 robot's weight reduction system allows for lateral weight shifting to reduce the weight on the affected side to help the patient develop a symmetrical gait pattern[31,32]. Some studies suggest robot improves stability by altering muscle coordination patterns, partial weight-bearing gait training results in changes in the average burst amplitude of the gastrocnemius and tibialis anterior muscles[33], with changes in the amount of body weight support and control of stride frequency, there is greater activation of the gastrocnemius and less activation of the tibialis anterior, and this change in muscle coordination patterns will provide better stability[34]. There is also support for gait robots to increase the firing rate of motor neurons without altering muscle strength[35]. In addition, the A3 robot's visual feedback and dystonia sensing system will have a beneficial effect on motor control in stroke patients. According to the view of Lam *et al*[36] scholars, the process of stroke patients restoring walking ability through robot-assisted gait training is an adaptive change. The improvement in the A3 group was the combined effect of multiple interventions including an exoskeleton robot, weight loss training, and visual feedback.

This study also had some limitations. The sample size was small and not representative of the training effect in the majority of stroke patients,. Second, due to the short observation period, we cannot know whether the 2-wk training effect is sustainable. In addition, we did not perform kinetic or electromyographic (EMG) data, nor did we have brain imaging such as electroencephalogram (EEG), near-infrared (NIR) imaging, or MRI, which may help to determine the mechanism of action of the lower limb robot. Third, the balance parameters and gait time parameters we used are probably not comprehensive enough; however, the available assessment tools are not precise enough for certain metrics (*e.g.*, hip, knee, and ankle mobility, which varies partially from patient to patient due to patient size and sensor positioning), and we have chosen the most precise metrics possible.

For prospects, we venture to speculate, based on the results of this study, that patients with subacute phase stroke will require at least 2 wk or more of lower extremity robotic intervention over 6 mo to achieve significant gait and balance improvements, which will need to be verified by further studies. In addition, future research is proposed to combine brain-computer interfaces, EEG, EMG, NIR, and MRI imaging to explore the mechanisms of robotics to improve gait and balance.

CONCLUSION

The 2-wk A3 robotic intervention combined with conventional lower extremity training significantly improved gait and balance in subacute stroke patients and was more effective than conventional ground walking. In addition, the efficacy of the lower extremity robot may take 2 wk or more to become apparent.

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FOOTNOTES

Author contributions: Liu ZC, Zhang LJ, and Liu HY designed the research study; Zhang LJ, Wen X, Peng Y, Hu W, and Liao H performed the study; Liu ZC and Zhang LJ analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Clinical Trials Study

Effect of dietary with Zhibai dihuang pills and gonadotropin-releasing-hormone-analogue on girls with precocious and rapidly progressive puberty

Xue-Mei Wang, Wei Li, Liu-Qing Yang, Rui Luo, Chen-Chen Zhang

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Abstract

BACKGROUND

At present, the clinical mechanisms underlying precocious puberty remain unclear, making effective intervention for children experiencing this condition and rapidly progressive puberty essential.

AIM

To explore the effects of Zhibai dihuang pills and gonadotropin-releasing hormone analogue (GnRHa) on growth and ovarian function in girls with precocious puberty.

METHODS

The clinical data of 84 adolescent girls with precocious puberty and rapidly progressive puberty from February 2017 to August 2023 were retrospectively analyzed. Girls were divided into a control group and an observation group, with 42 cases in each group. The control group received diet intervention combined with GnRHa treatment, while the observation group received diet intervention combined with Zhibai dihuang pills + GnRHa treatment. Outcomes such as clinical efficacy, growth indicators, ovarian function, and adverse reactions were compared between the two groups.

RESULTS

The observation group showed superior clinical efficacy compared to the control group ($P < 0.05$). Prior to the intervention, no significant differences were found in growth or ovarian function between the groups ($P > 0.05$). Post-intervention, the observation group exhibited significantly lower rates in growth, height, and bone age, along with reduced levels of progesterone, testosterone, estradiol, prolactin, luteinizing hormone, and follicle-stimulating hormone compared to the control group ($P < 0.05$). The incidence of adverse reactions was similar across both

groups ($P > 0.05$).

CONCLUSION

Combining Zhibai dihuang pills with GnRHa and dietary intervention effectively improves growth, enhances ovarian function, and minimizes adverse reactions in adolescent girls with precocious and rapidly progressive puberty.

Key Words: Zhibai dihuang pills; Gonadotropin-releasing hormone analogue; Dietary intervention; Precocious puberty; Rapidly progressive puberty; Ovarian function

Core Tip: Combining Zhibai dihuang pills with gonadotropin-releasing hormone analogue (GnRHa) and dietary intervention significantly improves growth outcomes and ovarian function in girls with precocious and rapidly progressive puberty. In this study, girls treated with this combination showed lower rates of growth and bone age advancement, along with reduced levels of key hormones, compared to a control group receiving only GnRHa and diet intervention. This study highlighted the enhanced efficacy and safety of the combined treatment and provides a promising intervention for managing precocious puberty.

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INTRODUCTION

Precocious puberty is characterized by the early onset of puberty, occurring in girls before the age of 8 and in boys before the age of 9, typically resulting from abnormalities in the endocrine system. Rapidly progressive puberty describes a condition where the hypothalamic-pituitary-gonadal axis advances from the defined age of precocious puberty to the typical age of puberty onset, exhibiting an accelerated progression of sexual development and bone maturation[1]. Epidemiological studies have indicated that precocious puberty is relatively common in children, with an incidence rate of approximately 10%, making it the second most prevalent endocrine disorder[2]. The primary goals in treating precocious puberty and rapidly progressive puberty are to delay the onset and progression of secondary sexual characteristics and to improve adult height outcomes in affected children[3].

Compared to boys, girls exhibit a clearer gender identity concerning precocious puberty and rapidly progressive puberty, with a significantly higher incidence rate. The primary clinical manifestations in girls include premature breast development, early uterine and ovarian development, and early onset of menstruation[4,5]. Previous studies have shown that the presentation of precocious puberty depends on the degree of precocity, which may result in excessive skeletal growth and premature epiphyseal fusion, ultimately affecting normal development and leading to short stature. Additionally, precocious puberty and rapidly progressive puberty can have serious negative impacts on the psychological and psychosocial behaviors of affected children[6,7]. Given that the clinical mechanisms underlying precocious puberty are not fully understood, effective intervention for children experiencing these conditions is crucial.

Gonadotropin-releasing hormone antagonists, such as leuprorelin, are commonly used to treat children with precocious puberty. These drugs inhibit the release of sex hormones, thereby delaying the process of sexual development and preventing the premature closure of epiphyses, which can impact height development. Additionally, they can effectively reduce psychological issues, such as social withdrawal and feelings of inferiority, that affected children may experience[7,8]. Since treatment with leuprorelin requires a long duration, typically at least 2 years, to achieve the goal of improving adult height, some patients may experience slowed growth rates, necessitating additional growth hormone therapy. This not only increases the cost of treatment but also complicates the treatment process. Therefore, there remains a need for clinical exploration of alternative intervention methods[9]. Therefore, there remains a need for clinical exploration of alternative intervention methods. In addition, Meng *et al*[10] reported that a high-fat, high-calorie diet is a confirmed risk factor for precocious puberty. Dietary components can influence hormone levels in the body, and poor dietary habits may contribute to idiopathic central precocious puberty (CPP)[11]. This suggests that dietary intervention may have therapeutic effects on children with precocious puberty and rapidly progressive puberty. However, some patients may not achieve the desired therapeutic effect with dietary intervention alone. Moreover, gonadotropin-releasing hormone analogue (GnRHa) is expensive, and some patients experience adverse reactions such as redness and swelling, which can affect compliance. Clinically, it is believed that the incidence of precocious puberty is related to kidney abnormalities, with kidney deficiency and excessive fire being common causes. Treatment should focus on tonifying the kidney and reducing fire, with Zhibai dihuang pills being a representative drug. Zhibai dihuang pills have proven effective in treating precocious puberty, showing superior improvements in sex hormone levels and follicular diameter

compared to triptorelin. They have been increasingly used in the treatment of precocious puberty and related conditions in recent years. This study aims to observe the effects of combining Zhibai dihuang pills with GnRHa and rational dietary intervention on growth rate and ovarian function in girls with precocious puberty and rapidly progressive puberty, providing a reference for the treatment of children with these conditions.

MATERIALS AND METHODS

General information

This retrospective study included 84 girls with precocious puberty and rapidly progressive puberty admitted to our hospital between February 2017 and August 2023. The subjects were divided into two groups: A control group and an observation group, with 42 cases in each group. This study was approved by the Hospital Ethics Committee, and all procedures followed the ethical guidelines of the Helsinki Declaration regarding clinical research. Before enrollment, all subjects were informed of the research content and signed informed consent forms.

Inclusion and exclusion criteria

Inclusion criteria: Precocious puberty: (1) Diagnosis of precocious puberty according to the "Diagnosis and Treatment Consensus of CPP"[12], based on symptoms and signs; (2) The girl developed secondary sexual characteristics before the age of 8 and progressed according to the normal developmental procedure; (3) GnRH stimulated luteinizing hormone (LH) peak > 3.3-5.0 U/L, and LH peak/follicle-stimulating hormone (FSH) peak ratio > 0.6; and (4) The uterus is 3.4-4.0 cm, the volume of the unilateral ovary is ≥ 1-3 mL, and multiple follicles with diameter ≥ 4 mm can be seen. Rapidly progressive puberty: (1) Onset of the hypothalamic-pituitary-gonadal axis in girls aged 8-10 years, accompanied by accelerated sexual maturation (the interval from one Tanner stage to the next is shorter than 3-6 months); and (2) Accelerated bone age maturation (bone age exceeds actual age by more than 1 year).

Exclusion criteria: (1) Girls with secondary CPP after excluding other causes (such as adrenal disease, central nervous system disease); (2) Girls with organic diseases (such as uterine and ovarian dysplasia); (3) Girls with familial genetic diseases, metabolic diseases, and chromosomal abnormalities; and (4) Girls with incomplete clinical data.

Methods

Dietary intervention during the treatment period required patients to avoid consuming nutritional tonics, foods with high estrogen content, out-of-season vegetables, foods high in trace element zinc, and foods with high levels of preservatives and additives. In addition to dietary intervention, the control group was given leuprolide acetate microspheres for subcutaneous injection (manufacturer: Shanghai Lisheng Pharmaceutical Co., Ltd.; approval number: National Drug Approval No. 220826; specification: 3.75 mg), 3.75 mg per dose, administered once every 28 days. The initial dose of leuprorelin microspheres was 80 to 100 μg/kg, administered once every 4 weeks[13]. The treatment regimen was adjusted based on the child's response, with follow-up examinations conducted every 6 months. Observation group was treated with Zhibai dihuang pills (Jiuzhitang Co., Ltd., National Drug Approval No. Z20023069; specification: 1.7 g per 10 pills) in addition to the control group regimen. Zhibai dihuang pills were administered at a dose of 8 pills per time, 3 times a day, for a course of 4 weeks, with continuous treatment for 6 months.

Observation indicators

Clinical efficacy: The effectiveness of treatment was determined by the degree of reduction in breast nodules and the development of the uterus and ovaries in children after intervention. The criteria for evaluation were as follows: (1) Cure: Breast nodules almost disappeared, and the development of the uterus and ovaries stagnated; (2) Marked effect: Breast nodules decreased by more than 50%, and the development of the uterus and ovaries stagnated; (3) Effective: Breast nodules decreased by 30% to 50%, and the development of the uterus and ovaries stagnated; and (4) Ineffective: No significant reduction or continued enlargement of breast nodules, and no significant improvement or continued development of the uterus and ovaries. Total effective rate = cure rate + marked effect rate + effective rate.

Growth indicators: Comparison of growth indicators such as growth rate, height, and bone age between the two groups of children. Formula for calculating growth rate is: Growth rate (cm/year) = {[difference in height between two measurements (cm)]/[difference in time between two measurements (months)]} × 12 (months/year).The Greulich and Pyle method was used to analyze the bone age of the patients.

Ovarian function: Blood samples (5 mL) were collected from the subjects before and after the intervention. The levels of progesterone (P), testosterone (T), estradiol (E2), prolactin (PRL), LH, and FSH in both groups were measured using radioimmunoassay.

Adverse reactions: The occurrence of adverse reactions during the intervention period in both groups of children, such as sweating, back pain, dizziness, and dry mouth, was recorded.

Statistical analysis

SPSS 22.0 software was used for data analysis. Measurement data were expressed as mean ± SD, and the independent sample *t*-test was used to compare differences between groups. Count data were expressed as rates, and χ^2 analysis was

Table 1 Basic clinical data of children in the two groups (mean ± SD)

Group		Control group	Observation group	t/χ^2	*P* value
Case (*n*)		42	42		
Age	Maximum	10	11	0.079	0.694
	Minimum	6	6		
	Average	8.79 ± 1.08	8.87 ± 1.17	0.354	0.443
Height (cm)	Maximum	141	144	3.977	0.051
	Minimum	113	111		
	Average	126.59 ± 2.52	125.34 ± 2.40	1.679	0.098
Body quality (kg/m^2)	Highest	20.69	21.38	0.760	0.308
	Lowest	15.35	15.30		

Table 2 Comparison of clinical efficacy between the two groups

Group	Control group	Observation group	t/χ^2	*P* value
Case (*n*)	42	42		
Healing	0	5		
Significant	17	25		
Effective	15	9		
Invalid	10	3		
Total effective rate, *n* (%)	32 (76.19)	39 (92.86)	17.163	0.001

used to compare differences between groups. A P value < 0.05 was considered statistically significant.

RESULTS

General clinical data of the two groups of children

As shown in Table 1, there was no statistically significant difference in basic clinical data such as height and weight between the two groups of children, indicating comparability (P > 0.05).

Comparison of clinical efficacy

After 6 months of intervention, the clinical efficacy of the observation group was higher than that of the control group, and the differences were statistically significant (P < 0.05) (Table 2).

Comparison of growth indicators

Before intervention, there was no statistically significant difference in growth and development indicators between the two groups of children (P > 0.05). After the intervention, the growth rate, height, and bone age indicators of girls with precocious puberty and rapidly progressive puberty in the observation group were significantly lower than those in the control group (P < 0.05). Specific numerical values can be seen in Table 3.

Comparison of ovarian function

Before intervention, there was no statistically significant difference in various ovarian function indicators between the two groups of children (P > 0.05). After 6 months of intervention, the levels of P, T, E2, PRL, LH, and FSH in the observation group were lower than those in the control group, with the differences being statistically significant (P < 0.05) (Table 4).

Comparison of adverse reactions

There was no statistically significant difference in the incidence of adverse reactions between the two groups of children (P > 0.05), as shown in Table 5.

Table 3 Comparison of growth indicators between the two groups of children (mean ± SD)

Group	Control group	Observation group	*t*	*P* value
Growth rate (%)				
Before intervention	4.56 ± 0.61	4.81 ± 0.75	1.715	0.090
After intervention	3.56 ± 0.59	2.25 ± 0.89	8.190	0.001
Height (cm)				
Before intervention	125.26 ± 3.00	125.11 ± 2.95	0.222	0.829
After intervention	133.44 ± 2.33	127.81 ± 2.43	10.934	0.001
Bone age (year)				
Before intervention	8.80 ± 0.50	8.91 ± 0.64	0.941	0.348
After intervention	9.24 ± 0.64	7.21 ± 0.33	18.836	0.001

Table 4 Comparison of ovarian function indicators between the two groups of children (mean ± SD)

Group	Control group	Observation group	*t*	*P* value
P (ng/mL)				
Before intervention	4.76 ± 1.60	4.83 ± 1.69	0.141	0.891
After intervention	2.94 ± 0.73	2.14 ± 0.64	5.466	0.001
T (nmol/L)				
Before intervention	6.78 ± 2.16	6.73 ± 2.22	0.148	0.881
After intervention	4.46 ± 1.44	3.11 ± 1.12	4.757	0.001
E2 (pg/mL)				
Before intervention	30.34 ± 5.72	30.85 ± 5.69	0.387	0.706
After intervention	18.76 ± 2.92	11.44 ± 2.75	11.814	0.001
PRL (ng/mL)				
Before intervention	12.76 ± 3.51	13.05 ± 3.64	0.370	0.712
After intervention	11.00 ± 2.54	8.93 ± 2.79	3.591	0.001
LH (U/L)				
Before intervention	3.16 ± 0.08	3.19 ± 0.08	0.569	0.572
After intervention	2.14 ± 0.36	1.51 ± 0.27	9.314	0.001
FSH (IU/L)				
Before intervention	15.22 ± 5.26	15.36 ± 5.15	0.123	0.913
After intervention	8.76 ± 2.57	6.27 ± 2.35	4.615	0.001

P: Progesterone; T: Testosterone; E2: Estradiol; PRL: Prolactin; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

DISCUSSION

Precocious puberty is an abnormal puberty development condition characterized by the premature appearance of puberty characteristics compared to children of the same age[14]. Due to differences in pathological mechanisms, precocious puberty is classified into central and peripheral types, each requiring distinct treatment approaches and having different prognoses[15,16]. The etiology of precocious puberty is complex, and the condition progresses rapidly. Without timely and effective treatment, it may lead to premature epiphyseal closure, early menstruation, breast development, and pubic hair growth, severely impacting the physical and mental health of affected children[5,17]. Therefore, accurate and timely diagnosis becomes crucial.

Here, the mechanism by which Zhibai dihuang pills inhibit precocious puberty involves multiple pathways. Zhibai dihuang pills contain ingredients like Rhizoma Anemarrhenae, Cortex Phellodendri, Radix Rehmanniae Preparata, Rhizoma Dioscoreae, Cortex Moutan, and Rhizoma Alismatis, which have anti-inflammatory and antioxidant properties,

Table 5 Comparison of adverse reactions between the two groups of children, *n* (%)

Group	Control group	Observation group	*Z*	*P* value
Case	42	42		
Sweat	1 (2.38)	0 (0)		
Back pain	1 (2.38)	0 (0)		
Dizziness	0	0		
Dry mouth	1 (2.38)	1 (2.38)		
Adverse reaction rate	3 (7.14)	1 (2.38)	0.216	0.641

helping to reduce oxidative stress and inflammatory responses, thereby modulating hormone levels[18]. Additionally, these pills may influence the expression of genes related to puberty onset and progression by downregulating the expression of ESR1 in the uterus and ovaries[18].

In this study, the clinical efficacy of the observation group was significantly higher than that of the control group, indicating the significant effectiveness of Zhibai dihuang pills combined with leuprorelin microspheres and dietary intervention in treating girls with precocious puberty. Compared to the control group, after treatment, the growth rate and bone age of children in the observation group were lower. Additionally, the observation group exhibited greater height, higher predicted adult height, lighter weight, and younger bone age than the control group. Research has shown that early control of rapid weight gain in children is beneficial for reducing the incidence of precocious puberty[19,20]. Additionally, after the intervention, the children in the observation group exhibited superior status in terms of height, weight, and bone age, suggesting that controlling the rate of weight gain may help reduce the risk of precocious puberty.

LH-releasing hormone (LHRH) is a peptide hormone primarily produced by the hypothalamus, which acts on the anterior pituitary gland to stimulate the release of LH and FSH[21]. Before puberty, the secretion of LH and FSH already exhibits a diurnal rhythm, with higher levels at night. In the early stages of puberty, LH levels increase only at night, while in the mid-late stages of puberty, LH levels increase both during the day and at night[22,23]. In this study, observations of ovarian function indicators in children revealed that after 6 months of intervention, the levels of P, T, E2, PRL, LH, and FSH in the observation group were lower than those in the control group. This indicates that Zhibai dihuang pills combined with leuprorelin microspheres and dietary intervention can suppress metabolic and hormone levels in affected children, thereby improving ovarian function. The combination of dietary intervention, Zhibai dihuang pills, and leuprorelin microspheres may regulate hormone levels in affected children through various mechanisms, restoring them to levels comparable to those of children of the same age and slowing down the maturation process of bone cells. Additionally, adverse reactions such as sweating, back pain, and dry mouth were observed in the control group, while in the observation group, except for one child experiencing dry mouth, no other significant adverse drug reactions were observed, indicating a higher level of safety in this treatment approach.

CONCLUSION

For girls with precocious puberty and rapidly progressive puberty, Zhibai dihuang pills combined with leuprorelin microspheres and dietary intervention demonstrate significant clinical efficacy. This intervention regimen positively regulates the growth rate and ovarian function of affected children. These findings suggest that controlling the rate of weight gain may help reduce the risk of precocious puberty and rapidly progressive puberty. Additionally, the sample size was relatively small and limited to a single hospital, which may affect the generalizability of our findings. Future studies should include larger, multi-center trials with extended follow-up periods to validate our findings.

FOOTNOTES

Author contributions: Wang XM contributed to the conceptualization, formal analysis, project administration, software, supervision, validation, visualization, writing-original draft, and writing-review & editing of this manuscript; Wang XM and Li W participated in the data curation; Wang XM, Li W, and Yang LQ took part in the investigation and methodology of this manuscript; Luo R and Zhang CC were involved in the resources.

Institutional review board statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Ma'anshan Maternal and Child Health Hospital.

Clinical trial registration statement: This study was registered at Ma'anshan Maternal and Child Health Hospital clinical trial registry. Hospital Clinical Trial Registry, Registration number: MASSFYBJY-LLWYH26.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Clinical efficacy, bone density, and follow-up in implant and orthodontic treatment for inclined adjacent teeth

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Abstract

BACKGROUND

Tooth defects can cause elongation of occlusal teeth, leading to insufficient repair space. The combination of dental implant restoration and orthodontic treatment of oblique adjacent teeth has a significant therapeutic effect.

AIM

To explore clinical efficacy, bone density, and follow-up of implant and orthodontic treatment for patients with inclined adjacent teeth.

METHODS

In total, 98 patients with oblique adjacent teeth were randomly assigned to implant restoration combined with orthodontic treatment (group A, n = 49) or to receive implant restoration alone (group B, n = 49). Changes in alveolar ridge bone density and apical bone density were observed before and after treatment in the two groups. Changes in chewing function and language function were compared between the two groups of patients. Follow-up lasted for 12 mo after repair to observe any adverse reactions in the oral cavity.

RESULTS

The clinical effective rates of group A and group B were 97.96% and 85.71%, respectively, with group A having a higher clinical effective rate than group B. After treatment, the bone density of the alveolar ridge and apical bone in both groups decreased compared to before treatment, while the chewing and language functions improved. The changes in various indicators in group A were more significant. After treatment, the satisfaction rate of group A (97.96%) was higher than that of group B (79.59%). The incidence of adverse reactions in group A (2.04%) was lower than that in group B (24.49%).

CONCLUSION
The amalgamation of implant restoration and orthodontic treatment for adjacent tilted teeth demonstrates notable clinical efficacy, diminishes alveolar bone resorption, and fosters patient functional rehabilitation while exhibiting negligible adverse reactions.

Key Words: Dental implant restoration; Orthodontic correction; Tilt adjacent teeth; Clinical curative effect; Alveolar bone mineral density

Core Tip: If dental defects are not repaired in a timely manner, adjacent teeth may tilt and shift. This causes elongation of the occlusal teeth, results in a lack of sufficient repair space, and leads to certain difficulties in the restoration of dentures. The combination of dental implant restoration and orthodontic treatment for tilted adjacent teeth has significant therapeutic effects, can reduce alveolar bone density, promote patient functional recovery, and is safe.

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INTRODUCTION

Dental defects resulting from caries, trauma, and congenital dysplasia are commonly encountered in clinical practice. These conditions not only significantly impact patients' masticatory function, speech articulation, and aesthetic appearance but also exert implications on the stomatognathic system and overall health[1]. Untimely repair of dental defects may lead to adjacent teeth misalignment and occlusal tooth elongation resulting in insufficient space for restoration, thereby posing challenges to denture rehabilitation[2].

With societal advancements and lifestyle changes coupled with an increased emphasis on self-image, there has been a rising trend in patients opting for dental restoration. Implant-supported dentures have emerged as a well-established and reliable modality for tooth replacement in contemporary dental care, offering advantages such as minimal invasiveness, reduced foreign body sensation, stability, and functional integrity. Nevertheless, not all patients meet the eligibility criteria for implantation[3]. In cases where implantation is hastily pursued without adequate tooth space, it can lead to improper occlusion and potential implant failure. Moreover, inadequate alveolar bone quality presents a significant challenge to successful implant therapy.

Bone augmentation and orthodontic intervention serve as pivotal approaches to address bone deficiencies[4]. The synergy between implant-supported dentures and orthodontic treatment is evident, with the latter facilitating sufficient space and optimal alveolar bone conditions for successful implant placement[5]. This study aimed to investigate the clinical efficacy and alveolar bone mineral density (BMD) outcomes of patients with inclined adjacent teeth who underwent combined implant restoration and orthodontic correction at our institution between May 2018 and January 2020. Subsequent patient follow-up and reevaluation were comprehensively analyzed to assess treatment effectiveness.

MATERIALS AND METHODS

A total of 98 patients with oblique adjacent teeth treated in General Hospital of Central Theater Command from May 2021 to January 2023 were randomly divided into the study group (group A) (n = 49) and control group (group B) (n = 49). Among them, there were 29 males and 20 females in the study group, aged 21-54 years, with an average age of 38.66 ± 14.46 years. In the control group, there were 30 males and 19 females, aged from 23-years-old to 53-years-old, with an average age of 39.49 ± 14.64 years. There were no significant differences in age and other basic data between the two groups (P > 0.05). Method patients in group B underwent solely implant restoration treatment.

Inclusion criteria

(1) Age between 20 years and 60 years; (2) Absence of neurological impairments allowing for treatment cooperation; (3) Presence of long-term tooth loss with adjacent dental inclination necessitating orthodontic intervention rather than denture implantation; (4) Approval from the hospital ethics committee adhering to medical ethics standards; and (5) Documented informed consent from patient and their family.

Exclusion criteria

(1) Pregnancy or lactation; (2) Coagulation dysfunction; (3) Hepatorenal or cardiac insufficiency; (4) Bone metabolic disorders; and (5) Inability to maintain oral hygiene independently.

Method

Preoperative X-ray images were obtained to assess the oral condition, particularly the relationship between the implant site and adjacent structures, aiding in the selection of appropriate implant systems and components. Prior to the procedure, patients received routine administration of cephalosporin, metronidazole, and other medications for prophylaxis, along with oral and maxillofacial region disinfection. Local anesthesia was administered before making an incision in the gingiva to expose the alveolar bone. High-speed mobile phones and ball drills were utilized to create holes in the alveolar bone, gradually expanding them to accommodate the implants. Implants were then carefully inserted into the prepared sockets, with meticulous attention paid to the protection of adjacent teeth. Subsequently, dentures were fitted to optimize the maxillary arch alignment. Patients were instructed on oral hygiene practices, and stitches were typically removed 1 wk post-implantation.

Patients in group A received a comprehensive treatment approach involving both implant restoration and orthodontic intervention. Initially, X-ray imaging was employed to assess the extent and distribution of missing teeth. Following this, oral cleaning procedures were performed to prepare the mouth for subsequent treatment. Orthodontic techniques were then utilized to rectify malocclusions, focusing on aligning both upper and lower dentitions. Additionally, adjustments were made to the positions of abutment teeth, canines, and other adjacent teeth to optimize dental occlusion and alignment. Following the completion of orthodontic treatment, patients underwent implant restoration procedures to replace missing teeth.

Observation index clinical efficacy assessment encompassed the evaluation of therapeutic outcomes in both study groups and were categorized as effective, partially effective, and ineffective. Noteworthy effectiveness was characterized by stable implant fixation, aesthetically pleasing and satisfactory restorations, and restored normal masticatory function. Partial effectiveness denoted stable implant fixation with occasional loosening, improved restoration aesthetics, and satisfactory enhancement of masticatory function. Ineffectiveness was defined by implant damage or loosening, lack of improvement in masticatory function, and the presence of inflammation.

Alveolar BMD alterations, specifically at the crest and apical regions, were quantified *via* X-ray imaging to assess changes before and after treatment in both study cohorts. The masticatory and language functions of participants were evaluated utilizing the Eichner classification system, with a maximum score of 10 indicating optimal patient recovery. Higher scores correlated with improved functional outcomes. Patient satisfaction was gauged using a self-designed satisfaction assessment tool, with ratings including "very satisfied," "satisfied," and "dissatisfied." Scores ranged from 0 to 100, with ratings above 85 indicative of very high satisfaction, 55-85 indicating satisfaction, and scores below 55 representing dissatisfaction. Follow-up examinations were conducted after 12 mo post-treatment to monitor the occurrence of oral adverse reactions. Patients were advised to prioritize oral hygiene and maintain regular dental cleanings to optimize oral health outcomes.

Statistical analysis

In this study, a comparison of clinical efficacy, satisfaction, and the incidence of adverse reactions between group A and group B was conducted using the χ^2 test, with results expressed as n (%). The alveolar BMD, masticatory function, and language function of both groups were evaluated using independent sample t-tests, with results presented as mean ± standard deviation. Statistical analyses were performed using SPSS 18.0 (IBM Corp., Armonk, NY, United States), with significance determined at $P < 0.05$.

RESULTS

The clinical effective rates of group A and B were 97.96% and 85.71%, respectively, and the clinical effective rate of the group A was higher than group B (Table 1). After treatment, the alveolar crest BMD and apical BMD in the two groups were reduced than before treatment, and those in group A were reduced more than group B (Table 2). After treatment, the masticatory function and language function of the two groups were increased than those before treatment. The masticatory function of group A was higher than group B (Table 3). After treatment, the satisfaction of patients in group A and group B was 97.96% and 79.59%, respectively, and the satisfaction in group A was higher than group B (Table 4). There was only 1 case of implant loosening in group A, and the incidence of adverse reaction was 2.04%. In group B, there were 41 cases of gingivitis, 41 cases of periodontal discomfort, 7 cases of implant loosening, and 3 cases of root resorption. The incidence of adverse reaction was 24.49%. The level in group A was decreased compared to group B (Table 5).

DISCUSSION

Dentition defects denote variations in the number of missing teeth across different regions of the dentition, thereby compromising the patient's masticatory function, speech articulation, and aesthetic appearance. Investigations reveal persistently high prevalence rates of dentition defects and periodontal diseases. Untimely restoration of missing teeth may precipitate adjacent teeth tilting and shifting towards the edentulous spaces, while opposing teeth may elongate due

Table 1 Proportion of clinical efficacy

Group	*n*	Significant effect	Effective	Invalid	Total effective
A	49	35 (71.43)	13 (26.53)	1 (2.04)	48 (97.96)
B	49	27 (55.10)	15 (30.61)	7 (14.29)	42 (85.71)
χ^2					4.900
P value					0.027

Data are *n* (%). Group A: Implant restoration combined with orthodontic treatment; Group B: Implant restoration alone.

Table 2 Comparison of alveolar bone mineral density

Group	*n*	Alveolar crest parietal bone mineral density in g/cm²		*t* value	*P* value	Apical bone mineral density in g/cm²		*t* value	*P* value
		Before treatment	After treatment			Before treatment	After treatment		
A	49	350.28 ± 25.37	327.36 ± 26.60	4.365	< 0.001	332.23 ± 11.58	308.09 ± 12.62	9.866	< 0.001
B	49	350.54 ± 23.63	339.17 ± 25.16	2.306	0.023	331.28 ± 14.73	300.04 ± 15.75	10.141	< 0.001
t value		0.053	2.258			0.355	2.792		
P value		0.958	0.026			0.723	0.006		

Data are mean ± standard deviation. Group A: Implant restoration combined with orthodontic treatment; Group B: Implant restoration alone.

Table 3 Comparison of masticatory function and language function

Group	*n*	Time	Masticatory function	Language function
A	49	Before treatment	4.68 ± 1.24	4.82 ± 0.98
		After treatment	9.39 ± 0.39[a,b]	9.25 ± 0.22[a,b]
B	49	Before treatment	4.75 ± 1.36	4.85 ± 1.03
		After treatment	7.13 ± 0.40[a]	7.05 ± 0.47[a]

Data are mean ± standard deviation.
[a]*P* < 0.05 *vs* pre-treatment.
[b]*P* < 0.05, indicated a significant difference between the study group and the control group. Group A: Implant restoration combined with orthodontic treatment; Group B: Implant restoration alone.

Table 4 The proportion of patient satisfaction

Group	*n*	Very satisfied	Satisfied	Not satisfied	Satisfaction
A	49	39 (79.59)	9 (18.37)	1 (2.04)	48 (97.96)
B	49	23 (46.94)	16 (32.65)	10 (20.41)	39 (79.59)
t value					8.295
P value					0.004

Data are *n* (%). Group A: Implant restoration combined with orthodontic treatment; Group B: Implant restoration alone.

Table 5 Proportion of oral adverse reactions

Group	*n*	Gingivitis	Periodontal discomfort	Implant loosening	Root resorption	Total
Total	49	0 (0.00)	0 (0.00)	1 (2.04)	0 (0.00)	1 (2.04)
B	49	1 (2.04)	1 (2.04)	7 (14.29)	3 (6.13)	12 (24.49)
χ^2						10.731
P value						0.001

Data are *n* (%). Group A: Implant restoration combined with orthodontic treatment; Group B: Implant restoration alone.

to lack of occlusal contact, resulting in occlusal discrepancies, food impaction, and potential periodontal tissue damage [6]. Furthermore, dental and skeletal atrophy may ensue, leading to facial asymmetry and consequent impairment of masticatory function and nutrient absorption[7]. Such conditions exert a significant impact on the patient's oral and maxillofacial complex as well as overall systemic health.

As social and economic advancements continue alongside progress in medical science and technology and with an evolving clinical repair ethos, there is a growing patient inclination towards aesthetically pleasing, minimally invasive treatment modalities. In contrast to conventional fixed and removable partial dentures, implant restoration offers distinct advantages including minimal tissue disruption, reduced foreign body sensation, stability, and optimal functionality. Furthermore, implant restoration facilitates superior aesthetic outcomes, occlusal function, and physiological efficacy while preserving the integrity of adjacent teeth. Consequently, it has emerged as a well-established and dependable method for edentulous reconstruction in contemporary dental care[8,9].

Nevertheless, not all patients meet the criteria for implantation adaptation. The decision for repair often hinges on aesthetic or functional concerns arising from missing teeth, typically manifesting with symptoms such as narrowed interdental spaces due to adjacent tooth displacement or occlusal tooth intrusion as well as an increase in scattered spaces, among others. Failure to address these issues promptly may impede subsequent treatment steps. Some researchers posit that establishing a harmonious occlusal relationship is pivotal in preventing bone resorption and occlusal trauma in implant-supported restorations[10]. Consequently, even in cases where implantation and repair are deemed necessary, achieving optimal harmony between function and aesthetics remains challenging. Hence, orthodontic intervention targeting inclined adjacent teeth and depressed elongated molars becomes essential to create adequate space and establish a favorable occlusal relationship for restoration.

Orthodontic measures serve to close interdental gaps, realign adjacent teeth towards edentulous spaces, and augment implant placement areas. Concurrently, implant therapy facilitates denture restoration, thereby fulfilling corrective and aesthetic objectives. This integrated approach effectively enhances patients' oral function, promoting overall oral health and well-being[11,12].

This study found that orthodontic intervention combined with implant therapy was minimally invasive, which can reduce the damage caused by grinding tooth tissue and reduce the trauma of occlusal by depressing the extended teeth, restoring the distance between the jaws and the gingiva and improving the efficiency and life of the implant[13]. The results of this study found that implant restoration combined with orthodontic treatment of inclined adjacent teeth had an obvious clinical effect, improved patient dental aesthetic satisfaction, and reduced the probability of adverse reactions.

Patients with dental defects often present with varying degrees of alveolar bone destruction, resulting in diminished bone mass, reduced periodontal ligament area, and alveolar ridge atrophy. These anatomical challenges pose significant obstacles to orthodontic interventions. Research indicates that during orthodontic tooth movement, the rate of alveolar bone resorption accelerates, leading to increased tooth mobility[14]. The health status of alveolar bone can be reflected by many aspects, among which BMD is an important index. BMD refers to the unit bone volume and the average bone mineral content of the noodle machine, which is not only an important index to reflect the cooling but also a sensitive index to reflect the severity of the disease[15].

The results of this study showed that implant restoration combined with orthodontic treatment of inclined adjacent teeth could reduce the BMD of the alveolar crest and apical area, improve the masticatory function and language function, and promote the recovery of patients. Implant restoration combined with orthodontic treatment of inclined adjacent teeth can play a significant clinical effect, reduce alveolar BMD, and promote the functional recovery of patients. After restoration, it was found that there were no obvious adverse reactions in implant restoration combined with orthodontic treatment.

CONCLUSION

The findings of this study demonstrated that the combination of implant restoration and orthodontic correction in patients with adjacent malocclusion teeth yielded superior clinical efficacy, improved alveolar bone density, enhanced masticatory and language functions, and reduced incidence of adverse reactions compared to implant restoration therapy alone. This method merits widespread clinical application. However, due to the limited number of participants, statistical significance may be affected, potentially reducing the reliability and representativeness of the results. Future directions

may involve multicenter studies recruiting participants from various regions to ensure sample diversity and result generalizability.

FOOTNOTES

Author contributions: Yang Y performed the majority of experiments, wrote the manuscript, and served as scientific advisor; Zhou SC and Ma YH designed the study and revised the manuscript; Wang X contributed to analytical tools; Dong QS and Yang Y participated to the collection of the human material; Ma YH was the guarantor.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Information-motivation-behavioral guided nursing for stroke patients with pulmonary dysfunction: A randomized controlled trial

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Abstract

BACKGROUND

Patients with stroke frequently experience pulmonary dysfunction.

AIM

To explore the effects of information-motivation-behavioral (IMB) skills model-based nursing care on pulmonary function, blood gas indices, complication rates, and quality of life (QoL) in stroke patients with pulmonary dysfunction.

METHODS

We conducted a controlled study involving 120 stroke patients with pulmonary dysfunction. The control group received routine care, whereas the intervention group received IMB-model-based nursing care. Various parameters including pulmonary function, blood gas indices, complication rates, and QoL were assessed before and after the intervention.

RESULTS

Baseline data of the control and intervention groups were comparable. Post-intervention, the IMB model-based care group showed significant improvements in pulmonary function indicators, forced expiratory volume in 1 sec, forced vital capacity, and peak expiratory flow compared with the control group. Blood gas indices, such as arterial oxygen pressure and arterial oxygen saturation, increased significantly, and arterial carbon dioxide partial. pressure decreased significantly

in the IMB model-based care group compared with the control group. The intervention group also had a lower complication rate (6.67% *vs* 23.33%) and higher QoL scores across all domains than the control group.

CONCLUSION

IMB model-based nursing care significantly enhanced pulmonary function, improved blood gas indices, reduced complication rates, and improved the QoL of stroke patients with pulmonary dysfunction. Further research is needed to validate these results and to assess the long-term efficacy and broader applicability of the model.

Key Words: Cerebrovascular accident rehabilitation; Respiratory function tests; Nursing methodology research; Behavioral medicine; Quality of life

Core Tip: Our study examined the impact of information-motivation-behavioral (IMB) model-based nursing on stroke patients with pulmonary dysfunction. The findings revealed that IMB care significantly improved pulmonary function and blood gas indices, reduced complications, and improved quality of life. The results highlight the potential of the IMB model to transform nursing practice and patient outcomes in cerebrovascular accident rehabilitation.

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INTRODUCTION

Stroke, classified as either ischemic or hemorrhagic, is a significant global health burden and a leading cause of long-term disability. The global incidence has witnessed an upward trend, largely attributed to evolving lifestyle factors[1,2]. Ischemic strokes caused by cerebral infarction are more prevalent than their hemorrhagic counterparts and have seen considerable advancement in clinical management over the years[3]. Despite this progress, stroke remains an enduring illness, often with permanent neurological deficits and associated complications such as dysphagia, cognitive impairment, and pulmonary dysfunction that contribute to diminished quality of life (QoL)[4]. Regrettably, dysphagia and cognitive impairment have historically dominated the clinical focus and pulmonary dysfunction has been overlooked. Pulmonary dysfunction post-stroke refers to a range of respiratory complications that can arise after a cerebrovascular event. This may encompass decreased lung volumes, impaired gas exchange, reduced respiratory muscle strength, and ineffective airway clearance. These dysfunctions can result from a combination of neurological deficits affecting respiratory control, immobilization, and secondary complications like aspiration due to dysphagia. Studies have shown that stroke patients are at an increased risk of developing respiratory infections, atelectasis, and other complications that can lead to prolonged hospital stays and diminished QoL[5]. The significant repercussions of post-stroke pulmonary dysfunction make early identification and management imperative. However, post-stroke pulmonary dysfunction is not uncommon and poses a significant threat to pulmonary health, precipitating severe complications such as respiratory failure, with far-reaching implications on overall well-being[6]. This highlights the urgent need for a more robust and targeted focus on respiratory function in the clinical management of stroke patients, with the ultimate goal of improving pulmonary rehabilitation and QoL[7-9].

The information-motivation-behavioral skills (IMB) model of guided nursing care is a promising and innovative approach to address this unmet need. This model, characterized by interventions that involve information, motivation, and behavioral skills, allows comprehensive health guidance. The patient-centric approach ensures superior quality of care and has demonstrated promising results despite its relative novelty in clinical practice[9-11]. Although it has been widely adopted for the management of diverse health conditions, most research on the application of the IMB model involves patients with post-stroke cognitive impairment, post-stroke dysphagia, and cerebral hemorrhage. However, the application and effectiveness of this model in the context of stroke-induced pulmonary dysfunction is underreported[9]. This research gap necessitates further exploration and understanding of how the IMB model can guide nursing care and impact pulmonary function rehabilitation in patients with post-stroke pulmonary dysfunction.

Building on this context, our study aimed to contribute to the ongoing research in this field by investigating the effects of IMB-model-based guided nursing care on pulmonary function rehabilitation in stroke patients. We hypothesized that IMB-model-based guided nursing care would significantly improve pulmonary function, enhance blood gas indices, reduce complication rates, and improve QoL in stroke patients with pulmonary dysfunction. Our findings aim not only to fill the existing research gap, but also to provide valuable clinical insights that can improve nursing practice and patient outcomes in this underserved patient population.

MATERIALS AND METHODS

Study design

With the approval of the Yancheng First Hospital Affiliated to Nanjing University School of Medicine's Medical Ethics Committee (2021-059), we initiated the process of selecting stroke patients with pulmonary dysfunction treated at the hospital from May 2021 to December 2022 as study participants in this randomized controlled trial. Our inclusion criteria were: (1) Confirmed diagnosis of stroke (including cerebral infarction and cerebral hemorrhage); (2) First episode during the recovery period of stroke; (3) Impaired lung function characterized by notable deviations in parameters such as forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), especially when considering the FEV1/FVC ratio in relation to established norms from clinical literature on respiratory complications; (4) Clear consciousness; and (5) Voluntary signing of the informed consent form. Potential participants were then assessed for eligibility. Those who met any of the following criteria were excluded: (1) Comorbidity with other severe nervous system disease; (2) Presence of cardiovascular disease; (3) Existing mental disorder; and (4) Inability to communicate normally. Following evaluation and application of the exclusion criteria, 120 eligible patients were randomized a control group and an intervention group, each consisting of 60 patients. Patient selection and allocation are illustrated in Figure 1.

Nursing intervention

Routine care was administered to the control group and included: (1) Health education and psychological intervention that introduced basic disease knowledge to patients, regularly monitored their emotional state, emphasized the importance of maintaining a positive attitude toward disease improvement, and used verbal soothing techniques to eliminate adverse psychological conditions. Family members were also instructed to encourage the patient to remain optimistic; (2) Dietary guidance by diet plans designed according to the patient's condition, emphasizing dietary restrictions, the importance of nutrition supplementation, and suggesting a light diet; (3) Regular sputum aspiration performed following the doctor's orders was followed by oxygen administration, generally for 2 min; and (4) Turning and. gentle back-tapping by the nursing staff once every 3 h to prevent secondary injuries, each session lasting 5-10 min. This was done 30 min before meals or 2 h after meals. The care was provided throughout the hospital stay.

The intervention group was given an IMB-model-based nursing intervention that included: (1) An informational intervention during which the medical staff engaged in regular communication with patients and their families, emphasizing targeted health education. The educational approach systematically addressed the etiology, clinical manifestations, risks, and preventive measures associated with post-stroke pulmonary dysfunction. Special emphasis was given to precautions during hospitalization and post-discharge. Guidance was also provided on adapting to a suitable lifestyle, dietary habits, the medication regimen, and engaging in respiratory muscle training exercises, including inspiratory muscle training and breathing retraining[5]; (2) A motivational intervention performed by nurses who introduced the prognosis of post-stroke pulmonary dysfunction, encouraged patients to set recovery goals, and provided positive psychological guidance. Rehabilitation case studies were used to boost confidence in recovery. Furthermore, emotional support from family members is also essential; and (3) Behavioral skills intervention that included deep breathing training in which patients were guided to engage in deep breathing exercises 2-3 times daily for 10 min each time. The exercise included slow, deep inhalation, followed by a 2-3 sec breath hold, followed by exhalation. Band-chest abdominal breathing intervention involved fastening strap around the chest and then inhaling deeply while expanding the abdomen, holding the breath for 1-2 sec and then exhaling. The exercise was repeated 3-5 times daily for approximately 3 mi each time. In relaxation training, patients were instructed to relax their muscles consciously to alleviate tension. During the exercise, the room was kept quiet with soft lighting, and light music was played. Patients were in a supine or semi-sitting position, closed their eyes, and consciously and systematically relaxed their muscles. This exercise was conducted twice daily for approximately 10 min each session. For posture control training patients were guided to frequently change their position, with sitting, standing, lying down, elbow stretching, and knee bending, to enhance their motor skills and respiratory function. The exercise was conducted once daily for 30-50 minutes. Complication prevention involved informing patients of potential complications and prevention methods. They were encouraged to exercise more, learn more about health-related knowledge, intensify self-health-condition monitoring, and informing the doctor promptly if any complication was observed.

Outcome measures

The primary observational indicators were: (1) Pulmonary function indicators, including FEV1, FVC, and peak expiratory flow (PEF) measured both before and after nursing care using a SENSOR MEDIC-6200 volumetric scanner; (2) Blood gas analysis by arterial oxygen pressure (PaO_2), arterial oxygen saturation (SaO_2), and arterial carbon dioxide pressure ($PaCO_2$) measured before and after nursing care using a Medica blood gas analyzer, (3) Complications that occurred during the hospital stay; (4) QoL was assessed by the SF-36 scale before and after nursing care; and (5) Nursing satisfaction was rated by patients on the day of discharge as very satisfied, somewhat satisfied, or not satisfied using a questionnaire.

Statistical analysis

Statistical analysis was performed using IBM SPSS Windows version 26.0. Quantitative data were reported as means ± SD, and between-group comparisons were made using independent sample *t*-tests. For categorical data, between-group comparisons of proportions between were performed using the χ^2 test. Ranked data were analyzed using the Wilcoxon rank-sum test for two independent samples. Statistical significance was set at $P < 0.05$.

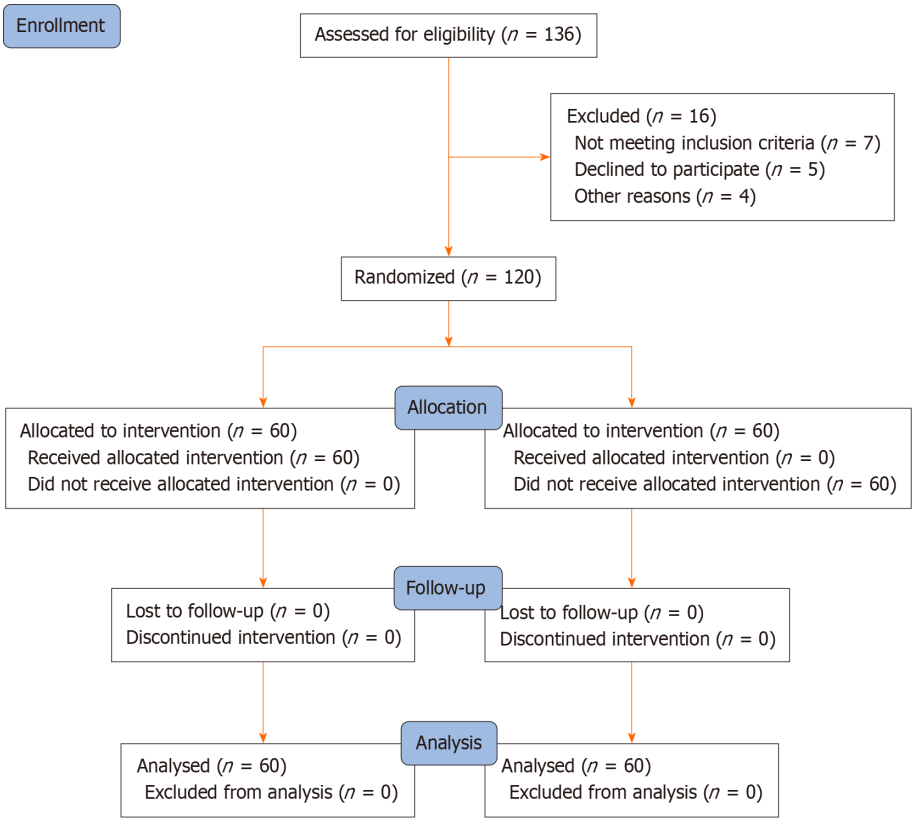

Figure 1 CONSORT flow diagram of patient selection and allocation.

RESULTS

Participant analysis

Our study included 120 stroke patients with pulmonary dysfunction. The patients were divided into observation and control groups of 60 each. The baseline data were similar, with the study groups well matched in age (P = 0.588), body mass index (P = 0.823), stroke duration (P = 0.885), pulmonary dysfunction duration (P = 0.941), and years of education (P = 0.759), ensuring between-group comparability. There were no statistically significant between-group differences of the baseline data (P > 0.05) (Table 1).

Comparison of pulmonary function indicators

Before the nursing intervention, there were no significant differences (P > 0.05) between the observation and control groups in terms of pulmonary function indicators, such as FVC, FEV1, and PEF. The measurements showed post-intervention improvement of FVC, FEV1, and PEF in both groups. However, the improvement in all three parameters was significantly greater in the intervention group than in control group (P < 0.001). This reveals the effectiveness of the nursing intervention, particularly in the intervention group, in enhancing pulmonary function. The results are shown in Table 2.

Comparison of blood gas analysis indicators between the two groups

Table 3 is a comparative analysis of the blood gas indicators in the observation and control groups, both pre- and post-nursing interventions. It shows improvement of PaO_2, $PaCO_2$, and oxygen saturation SaO_2 in both groups following the intervention. The intervention group had significant post-intervention increases of PaO_2 and SaO_2 and a decrease in $PaCO_2$ compared with the control group. These differences were statistically significant, suggesting that the nursing intervention had a more substantial positive effect on the blood gas parameters in the intervention group.

Comparison of complication rates

The monitored complications included aspiration, pulmonary atelectasis, pulmonary infection, and shoulder-hand syndrome. Following the nursing intervention, the intervention group experienced fewer complications than the control group, with overall incidence rates of 6.67% and 23.33%, respectively. This finding highlights the efficacy of nursing interventions in reducing the occurrence of complications, thereby enhancing patient care and recovery (Table 4).

Comparison of quality of life scores between the two groups

Table 5 shows the quality of life scores across eight different domains of patients in the observation and control groups before and after nursing care. Each domain was considered as pre- and post-nursing care. After the nursing intervention,

Table 1 Comparison of baseline characteristics between the intervention and control groups

Group	Number of cases	Sex, male/female	Age, years	Body mass index	Stroke duration, days	Pulmonary dysfunction duration, days	Education years
Intervention	60	32/28	68.60 ± 5.77	24.89 ± 3.57	28.64 ± 3.57	25.58 ± 2.23	9.32 ± 1.26
Control	60	35/25	68.90 ± 5.88	25.01 ± 3.65	28.70 ± 3.62	25.73 ± 2.29	9.37 ± 1.30
t value	-	0.349	0.266	0.19	0.096	0.355	0.16
P value	-	0.588	0.823	0.885	0.941	0.759	0.494

Table 2 Comparison of pulmonary function indicators in both groups

Group	Number of cases	FVC pre-intervention, L	FVC post-intervention, L	FEV1 pre-intervention, L	FEV1 post-intervention, L	PEF pre-intervention, L/s	PEF post-intervention, L/s
Intervention	60	2.38 ± 0.19	3.78 ± 0.25	1.78 ± 0.16	3.26 ± 0.19	5.27 ± 0.32	7.25 ± 0.25
Control	60	2.42 ± 0.21	3.07 ± 0.22	1.80 ± 0.19	2.28 ± 0.16	5.24 ± 0.36	5.83 ± 0.23
t value	-	0.868	16.605	0.665	30.908	0.499	32.288
P value	-	0.43	< 0.001	0.553	< 0.001	0.665	< 0.001

FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; PEF: Peak expiratory flow.

Table 3 Comparison of blood gas analysis indicators in t groups

Group	Number of cases	PaO_2 pre-intervention, mmHg	PaO_2 post-intervention, mmHg	$PaCO_2$ pre-intervention, mmHg	$PaCO_2$ post-intervention, mmHg	SaO_2 pre-intervention, %	SaO_2 post-intervention, %
Intervention	60	61.32 ± 6.35	79.21 ± 5.16	73.52 ± 5.46	58.14 ± 6.10	76.70 ± 7.15	93.66 ± 7.71
Control	60	61.24 ± 6.31	62.96 ± 5.34	73.60 ± 5.54	73.07 ± 5.84	77.34 ± 7.11	86.79 ± 7.62
t value	-	0.074	17.061	0.084	13.77	0.495	4.93
P value	-	0.941	< 0.001	0.933	< 0.001	0.671	< 0.001

$PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Arterial oxygen pressure; SaO_2: Arterial oxygen saturation.

Table 4 Comparison of complication incidence rates in both groups

Group	Cases, *n*	Aspiration	Pulmonary atelectasis	Pulmonary infection	Shoulder-Hand syndrome	Total cases	Incidence rate, %
Intervention	60	2	1	1	0	4	6.67
Control	60	3	3	2	6	14	23.33

the intervention group scores in all domains were significantly improved compared with the control group. This suggests the effectiveness of nursing care in enhancing patient QoL in various aspects, further highlighting the benefits of such interventions.

DISCUSSION

This study introduced a novel IMB-model-based nursing intervention tailored specifically for stroke patients with pulmonary dysfunction. It distinguished itself by systematically incorporating informational, motivational, and behavioral strategies. Our findings demonstrate that this comprehensive approach significantly improved pulmonary function and QoL compared to conventional care. Particularly noteworthy is the substantial enhancement of FEV1, FVC,

Table 5 Comparison of quality of life scores before and after nursing care in both groups

Group	Cases, *n*	Physical function		Social function		Mental health		Physiological role		Body pain		Energy		Emotional role		General health status	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Intervention	60	55.50 ± 4.15	78.05 ± 4.52	53.55 ± 4.89	77.30 ± 5.11	54.25 ± 4.94	78.35 ± 5.00	56.65 ± 4.10	78.76 ± 4.80	56.60 ± 4.24	80.12 ± 4.60	54.30 ± 4.93	79.30 ± 5.14	55.45 ± 4.95	78.80 ± 4.85	56.70 ± 4.08	79.05 ± 4.70
Control	60	55.46 ± 4.22	67.70 ± 4.56	53.81 ± 4.95	66.82 ± 5.40	54.58 ± 5.15	67.85 ± 5.00	56.90 ± 4.30	69.33 ± 4.60	56.05 ± 4.32	68.30 ± 4.56	53.90 ± 4.97	66.70 ± 5.25	55.60 ± 5.07	69.47 ± 5.00	56.98 ± 4.18	70.05 ± 4.60
t value		0.049	13.061	0.27	10.6	0.332	10.994	0.308	11.68	0.648	14.21	0.402	12.511	0.151	10.8	0.331	10.09
P value		0.961	0	0.788	0	0.741	0	0.759	0	0.518	0	0.689	0	0.881	0	0.741	0

and PEF values in the intervention group, which are crucial metrics for assessing pulmonary efficacy. Additionally, our intervention notably reduced the incidence of common complications such as aspiration and pulmonary atelectasis, further underlining its potential to mitigate secondary health issues frequently encountered in post-stroke management. These results underscore the pivotal role of structured nursing interventions in the rehabilitation of stroke patients and highlight the potential for significant improvement of clinical outcomes, emphasizing the need for their integration into routine clinical practice. This study not only fills a critical gap in stroke rehabilitation but also sets a foundation for future research to explore the longitudinal impact of such interventions on the trajectory of patient recovery.

Stroke is a cerebrovascular event of profound medical significance that occurs with varying degrees of severity in affected individuals. The dysfunctions span limb motor impairment, linguistic incapability, and cognitive deficits, which in turn impose a significant burden on patient QoL and elevate the responsibilities shouldered by their caregivers[12]. The ongoing clinical quest for effective treatment modalities for stroke encompasses two main categories: Conservative management and surgical intervention. The selection of these therapeutic strategies depends on an individual patient-specific clinical profiles. Stroke patients often present with severe and complex disease manifestations, harboring high risks even with immediate medical rescue. Despite expedited treatment, a large proportion of stroke survivors encounter numerous complications, aggravating their condition and undermining their prognosis[13,14].

In this context, high-quality nursing services have been recognized as significant contributors to improved treatment outcomes and improve disease conditions in stroke patients[15]. Therefore, it is imperative that the role of nursing services in treating these patients should be thoroughly emphasized. One commonly associated complication in post-stroke patients is cardiopulmonary functional impairment, with pulmonary dysfunction playing a significant role in overall morbidity[16,17]. This functional limitation often affects physical ability, hinders daily activity, and consequently has a substantial negative impact on their QoL, which increases their psychological distress. For stroke survivors with pulmonary dysfunction, interventions, including respiratory training, aerobic exercise in conjunction with isotonic limb muscle training, abdominal breathing training, and combined respiratory muscle-swallowing training, have been recommended. However, despite their standard operational procedures and long-standing application history, traditional nursing models have increasingly evident shortcomings in the face of evolving patient needs. The main criticisms have focused on the lack of flexibility and specificity, together with an insufficiently humane approach.

The IMB model-based nursing paradigm, characterized by a shift from a disease-centric to a patient-centric approach, marks a transformative phase in the healthcare of stroke patients with pulmonary dysfunction. This innovative model emphasizes the delivery of high-quality nursing services during hospitalization, thereby enhancing the patient's con-

dition and QoL. The IMB-model-based nursing paradigm involves interventions for patient information processing, motivational aspects, and behavioral skills. Strengthening nurse-patient communication to enhance a patient's understanding of their condition is a critical part of the informational intervention and aims to promoting their adherence to and outcomes of rehabilitation[18,19]. Motivational interventions primarily focus on providing positive psychological guidance to patients, instilling confidence in their ability to recover, and ensuring psychological wellbeing. Behavioral skill intervention, the crux of this nursing paradigm, involves guiding patients through systematic rehabilitation training and adopting targeted measures to prevent complications. The overarching goal is to gradually improve a patient's condition, ensure their physiological health, and enhance their QoL. Applying the IMB nursing model to patient care can effectively enhance physiological functions, thereby amplifying therapeutic outcomes, improving QoL, and offering advantages and utility over traditional care models.

The key findings of our study highlight the potential benefits of implementing the IMB skills model in nursing care for post-stroke patients with pulmonary dysfunction. The empirical evidence we accumulated points to the effectiveness of the model in fostering marked enhancement of pulmonary function and blood gas analysis indices. These improvements are not merely statistical figures; they represent substantial health advancements for patients who, in the aftermath of stroke, deal with complex and debilitating pulmonary dysfunction. The positive outcomes that we observed can be largely credited to the unique aspects of the IMB model, which includes informational and motivational interventions together with the development of key behavioral skills. The informational aspect of the IMB model empowers patients by providing comprehensive, comprehensible, and actionable health information. This approach aims to equip patients with knowledge about their condition, the importance of adhering to prescribed treatments, and the potential consequences of noncompliance.

Meanwhile, motivational interventions facilitate patients' internalization of the value and critical need to maintain their health and adhere to the prescribed regimen. These motivational interventions, which often involve counseling and emotional support, help patients foster the motivation to make positive health decisions. Behavioral skills interventions, the final component of the IMB model, focus on enhancing patients' capabilities to carry out necessary actions for their health maintenance. This might involve teaching them how to use medical equipment, adhere to medication schedules, or perform physical exercise. Our research further demonstrates that IMB-model-based nursing care significantly reduces the complication rates in patients. This reduction in complications can be seen as a testament to the IMB model's effectiveness as a proactive approach that not only manages the patient's existing conditions but also pre-empts potential complications. An additional significant finding of our study was the apparent beneficial effect of the IMB model on the QoL of patients. The model's emphasis on the psychological health of patients, its focus on mitigating negative emotions, and its efforts to boost the physical capabilities all contribute to enhancing QoL. This improved QoL is vital because it allows patients to regain a semblance of normalcy in their post-stroke, lives, enabling them to more effectively reintegrate into society.

Despite these promising results, our study had several limitations. The findings were influenced by specific geographic and healthcare contexts that may have affected generalizability. The sample was relatively small and the follow-up duration was short, which means that the long-term effects of the IMB model remain unclear. We also primarily focused on quantitative health outcomes by downplaying the subjective experience of patients with the IMB model. These areas underline the necessity for more comprehensive research to validate our findings and assess the full potential of the IMB model in various contexts.

CONCLUSION

In conclusion, this study suggests that IMB model-based nursing care effectively enhanced pulmonary function, improved blood gas analysis indices, and boosted the QoL of patients with post-stroke pulmonary dysfunction. Our findings highlight the potential of this model for reducing complication rates. However, given the study's inherent limitations, more comprehensive research is warranted to further validate these results and assess the model's long-term efficacy and broader applicability.

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FOOTNOTES

Author contributions: Peng X contributed to the conception of this study; Ni HQ and Liu YM made substantial contributions to literature search, data extraction, quality evaluation, data analysis, and manuscript preparation; Zhu JL contributed to enhancing the language, style, and protocol of this article; Peng X contributed to the analysis through constructive discussion; Bai YT revised and endorsed the final version of this manuscript.

Institutional review board statement: The Ethical Committee of Yancheng First Hospital Affiliated to Nanjing University School of Medicine endorsed all of the study's procedures (2021-059).

Clinical trial registration statement: This RCT was not registered due to urgent clinical needs and regional procedural barriers. Despite this, the trial was rigorously conducted, adhering to ethical and scientific standards with informed consent obtained. Future trials will be registered in advance to ensure transparency.

Informed consent statement: All the patients and their families included in this retrospective analysis provided written informed consent for publication.

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

Data sharing statement: The datasets generated and analyzed during this study are not publicly available due to the proprietary data of Yancheng First Hospital Affiliated to Nanjing University School of Medicine. However, they can be made available upon request. Interested parties should contact the corresponding author for access to the data.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Application of buried auricular point combined with Wenjing Sanhan prescription in arteriosclerosis obliterans patients with resting pain

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Abstract

BACKGROUND

Research on the combined use of ear acupoint embedding beans and warming meridians with cold-dispersing formulas for alleviating resting pain in patients with arteriosclerosis obliterans (ASO) remains limited.

AIM

To explore the therapeutic efficacy of auricular point embedding beans combined with Wenjing Sanhan prescription in alleviating resting pain in patients with lower-limb ASO.

METHODS

A total of 100 patients with ASO experiencing resting pain who were treated at our hospital from January 2022 to January 2023 were enrolled. They were randomly allocated into two groups using a double-blind approach. The control group was treated using a warming meridian with a cold-dispersing formula, while the study group received additional treatment with ear acupoint embedding beans. The clinical efficacy, ankle-brachial artery pressure ratio, hemorheological indicators, and traditional Chinese medicine symptom scores were compared between the two groups.

RESULTS

The clinical efficacy rate in the study group was significantly higher (94.00%) than that in the control group (72.00%, $P < 0.05$). Moreover, the ankle-brachial artery pressure ratio was significantly higher in the study group after treatment ($P < 0.05$). Hemorheological parameters, including whole blood viscosity, plasma viscosity (1.83 ± 0.11) mPa/s, fibrinogen levels (3.30 ± 0.21) g/L, platelet adhesion rate (49.87% ± 10.51%), and erythrocyte aggregation index (1.79 ± 0) were improved in the study group compared to the control group. In addition, the

scores for decreased skin temperature (1.41 ± 0.26), intermittent claudication (1.30 ± 0.20), and resting pain (1.23 ± 0.31) were significantly lower in the study group than those in the control group (all $P < 0.05$). The level of oxidative stress in the study group also exhibited significant improvement ($P < 0.05$), and the levels of inflammatory factors were considerably lower than those in the control group.

CONCLUSION
The combination of ear point embedding beans and Wenjing Sanhan prescription demonstrates promising clinical efficacy in alleviating resting pain associated with ASO.

Key Words: Embedding beans in ear acupoints; Prescription for warming channels and dispelling cold; Lower limb arteriosclerosis obliterans; Resting pain; Blood flow rheology; Curative effect

Core Tip: The combination of ear point embedding beans and Wenjing Sanhan prescription demonstrates promising clinical efficacy in alleviating resting pain associated with arteriosclerosis obliterans. It substantially improves the ankle-brachial artery pressure ratio, reduces hemorheological abnormalities and traditional Chinese medicine symptom scores, and alleviates resting pain.

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INTRODUCTION

Lower limb atherosclerosis obliterans (ASO) represents a prevalent vascular condition characterized by the narrowing or occlusion of lower limb arteries due to the formation of atherosclerotic plaques. Prolonged ischemia ensues, leading to the development of ASO over time[1,2]. Timely identification and effective management of atherosclerosis risk factors can delay disease progression and reduce ASO incidence rates. Currently, endovascular intervention surgery is a common therapeutic approach for ASO, offering advantages such as minimal trauma and reproducibility, thereby gaining widespread clinical acceptance[3]. However, patients undergoing interventional surgery are susceptible to complications such as restenosis[4]. Clinical manifestations of ASO onset frequently include symptoms such as numbness, discomfort, chills, and resting pain[5]. If severe ischemia affects the lower limbs, ischemic ulcers may occur. Resting pain manifests as a persistent, non-pulsatile discomfort in the limbs, frequently accompanied by intermittent claudication[6]. Middle-aged and older individuals comprise the majority of patients with ASO, with a prevalence rate reaching up to 17%[7]. These patients often have multiple comorbidities, and as the disease progresses, they experience pronounced resting pain, especially when lying flat and resting at night. This condition significantly affects patients' physical and mental health, resulting in decreased quality of life and increased medical expenses[8]. In traditional Chinese medicine (TCM), ASO is associated with "degeneracy" and "de rheumatism," attributed mainly to insufficient qi and blood, impaired blood circulation, and blocked meridians, leading to inadequate nourishment of the extremities. TCM approaches involving syndrome differentiation and treatment have demonstrated efficacy and gained widespread patient acceptance[9]. The earliest written records in the "Yin-yang Eleven-pulse Moxibustion Classic" highlight the significance of the "ear pulse." Similarly, the "Huangdi Neijing" documents the ear acupoints and their connections with various organs in the body, laying the theoretical groundwork and treatment modalities for addressing ailments through auricular therapy. However, research on the combined use of ear acupoint embedding beans and warming meridians with cold-dispersing formulas for alleviating resting pain in patients with ASO remains limited. Therefore, this study selected 100 patients with ASO experiencing resting pain to investigate the therapeutic outcomes[10,11].

MATERIALS AND METHODS

General information

A total of 100 patients with ASO experiencing resting pain underwent treatment at our hospital between January 2022 and January 2023. Among them, 52 patients exhibited blood stasis and meridian syndrome, while 48 presented with qi and yin deficiency syndrome. Employing a double-blind method, they were randomly allocated into two groups. The control group comprised 26 men and 24 women, aged 40 years to 74 years, with an average age of 56.30 ± 9.46 years. The duration of illness varied from 3 years to 9 years, with an average duration of 5.69 ± 1.45 years. The patients in this group had comorbidities such as hypertension and diabetes. In the study group, there were 26 men and 24 women, aged 40

years to 76 years, with an average age of 56.61 ± 9.52 years. The duration of illness ranged from 2 years to 10 years, with an average duration of 5.58 ± 1.36 years. Similar comorbidities were present in this group, including hypertension and diabetes. Informed consent forms were signed by the patients and their family members, and the study received approval from the internal ethics committee (Figure 1).

Inclusion criteria: Patients were included in the study based on the following criteria: meeting the relevant diagnostic criteria for ASO[12]; presence of ischemic resting pain as the primary symptom; conformance to the applicable standards for blood stasis syndrome outlined in "Traditional Chinese Medicine Surgery"[13]; Doppler ultrasound examination indicating a stenosis degree of ≥ 50%; normal mental state with the ability to communicate effectively.

Exclusion criteria: Patients who had recently undergone other relevant treatments; those with different malignant tumors; those with abnormalities in heart, liver, and kidney functions; those with coagulation disorders; and those with concurrent systemic diseases were excluded from the study.

Treatment methods

Both groups received conventional antihypertensive, hypoglycemic, and lipid-lowering treatments before the initiation of the study, supplemented by intracavitary intervention.

The control group underwent ear acupoint embedding bean treatment, as follows. One side was explored daily using an ear probe to locate acupoints, followed by disinfection with medical alcohol. A Wangbuliuxing seed was centered on medical tape and applied to specific acupoints, including Shenmen, sympathetic, subcortical of the cardiovascular system, hot acupoint, posterior sulcus of the lower limbs, and toe ear acupoint. Each acupoint received one seed, and pressure was applied using a method ranging from light to heavy, inducing sensations such as numbness, swelling, heat, and ear pain within the patient's tolerance range. This process was repeated 3-5 times daily, with 30-50 times presses each time, ensuring a time interval of at least 3 h. Seeds were replaced every other day, and bilateral auricles were treated.

The study group received the same ear acupoint embedding bean treatment as the control group, supplemented by the Wenjing Sanhan prescription, consisting of 5 g each of *Wuyao*, *Xiaofenxiang*, and *Myrrh*; 9 g each of *Xiangfu*, *Yujin*, *Puhuang*, and *Wulingzhi*; and 12 g each of Litchi seed, *Safflower*, *Angelica sinensis*, and *Fuzi* (prepared). This formula was administered in a water decoction of 300 mL divided into two doses (morning and evening), taken daily. The medicinal materials were soaked for 30 min before decoction. Both groups were treated continuously for 4 wk.

Evaluation criteria

TCM symptom score: Skin temperature reduction, intermittent claudication, and resting pain syndromes were scored according to the "Diagnosis and Treatment Criteria for Arteriosclerotic Occlusion"[10]. Scores were as follows: Skin temperature reduction in the lower limbs or feet: 0 points for no reduction, 1 point for mild reduction, and 2 points for significant reduction; Intermittent claudication: 0 points for none, 1 point for mild intermittent claudication, with the ability to walk a long distance (> 200 m) without experiencing claudication symptoms, 2 points for moderate intermittent claudication, appearing after walking a short distance (50-200 m), and 3 points for severe intermittent claudication: Appearing after walking a short distance (< 50 m); Resting pain: 0 points for none, 1 point for intermittent resting pain, without affecting sleep, 2 points for intermittent resting pain affecting sleep, and 3 points for persistent resting pain, with scores proportional to severity.

Hemorheology: Peripheral venous blood samples (5 mL) were collected from both patient groups 12 h before and after treatment. The samples were centrifuged at a rate of 3500 rpm with a radius of 0.2 mm for 10 min to separate the supernatant. Whole blood viscosity and plasma viscosity were measured using an automatic hemorheological analyzer (HT-100B; Zibo Hengtuo Analysis Instrument Co., Ltd., Shandong, China). The platelet adhesion rate was determined using the glass filter method. Fibrinogen levels were obtained using a fully automatic coagulation analyzer (RAC-030; Shanghai Yuyan Scientific Instrument Co., Ltd., Shanghai, China). The red blood cell aggregation index was measured using a fully automatic analyzer (U-3081; Shanghai Yudo Biotechnology Co., Ltd., Shanghai, China).

Oxidative stress: An additional 3 mL of peripheral venous blood was collected to measure the levels of malondialdehyde, superoxide dismutase, and myeloperoxidase using radioimmunoprecipitation technology.

Inflammatory factors: Another 3 mL of peripheral venous blood was collected to assess interleukin (IL)-8 and IL-6 levels using enzyme-linked immunosorbent assay (ELISA kit, batch number: XY-JCSJH-1140; Shanghai Xuanya Biotechnology Co., Ltd., Shanghai, China). C-reactive protein levels were determined using immunoturbidimetry.

Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, NY, United States) statistical software was used for data analysis. Measurement data conforming to normal distribution were described as mean ± SD, and a bilateral *t*-test was used to compare the means between the two groups. Percentages were calculated for categorical data, and inter-group comparisons were performed using the χ^2 test. A P value < 0.05 was considered statistically significant.

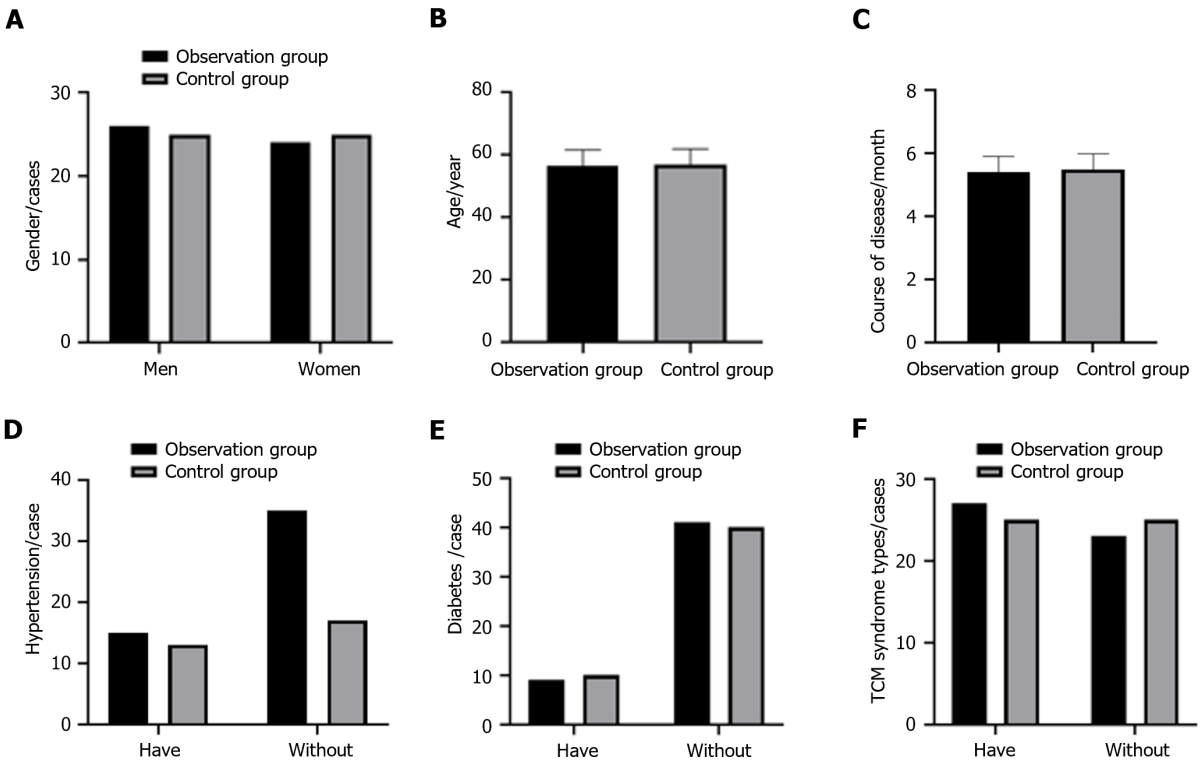

Figure 1 Comparison of two groups of data. A: Sex; B: Age; C: Course of disease; D: Hypertension; E: Diabetes; F: Traditional Chinese medicine (TCM) syndrome types.

RESULTS

Comparison of clinical efficacy between two groups

The study group exhibited a total clinical efficacy rate of 94.00%, significantly higher than the 72.00% observed in the control group ($P < 0.05$) (Figure 2).

Comparison of ankle/brachial artery pressure ratio between two groups

Post-treatment, the ankle-brachial artery pressure ratio in the study group surpassed that of the control group ($P < 0.05$) (Figure 3).

Comparison of ankle/brachial artery pressure ratio between two groups

After treatment, the ankle-brachial artery pressure ratio in the study group surpassed that of the control group ($P < 0.05$) (Figure 3).

Comparison of hemorheological indicators between two groups

In the study group, levels of various indicators such as whole blood viscosity (12.74 ± 2.06) mPa/s, plasma viscosity (1.83 ± 0.11) mPa/s, fibrinogen (3.30 ± 0.21) g/L, platelet adhesion rate (49.87% ± 10.51%), and red blood cell aggregation index (1.79% ± 0.20%) were significantly lower compared to the control group ($P < 0.05$) (Figures 4 and 5).

Comparison of TCM symptom scores between two groups

Following treatment, the study group demonstrated significantly lower scores for skin temperature reduction (1.41 ± 0.26), intermittent claudication (1.30 ± 0.20), and resting pain (1.23 ± 0.31) compared to the control group ($P < 0.05$) (Figure 6).

Oxidative stress indicators

The observed improvement in oxidative stress levels was more significantly pronounced in the study group than in the control group ($P < 0.05$) (Figure 7).

Inflammatory factor indicators

Levels of inflammatory factors in the study group were considerably lower than those in the control group ($P < 0.05$) (Figure 8).

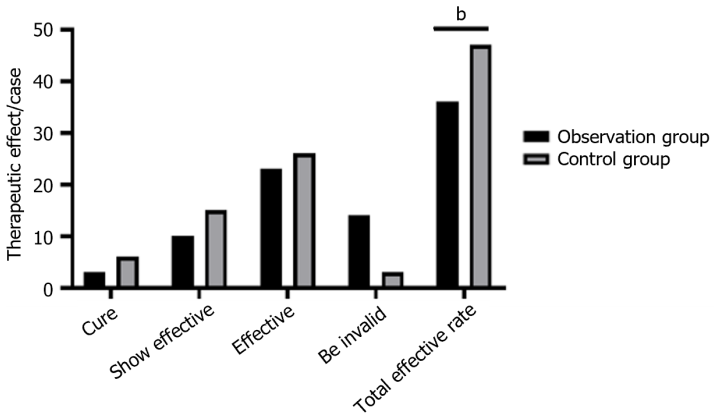

Figure 2 Comparison of clinical efficacy between the two groups. $^{b}P < 0.05$ indicates a statistically significant difference between the control group and the study group.

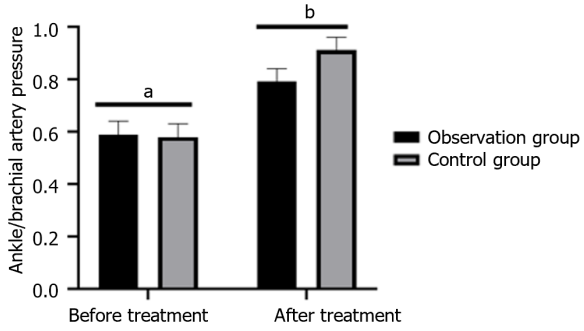

Figure 3 Comparison of ankle-brachial artery pressure ratio between two groups. $^{a}P > 0.05$ indicates no significant difference between the study and control groups; $^{b}P < 0.05$ indicates that the difference between the study and control groups was statistically significant.

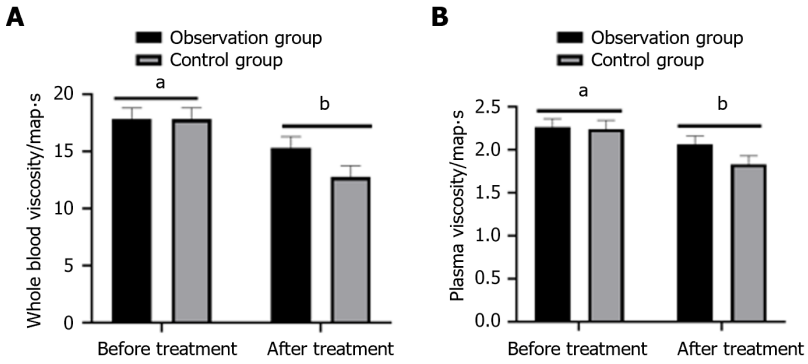

Figure 4 Comparison of hemorheological indicators between the two groups. A: Whole blood viscosity; B: Plasma viscosity. $^{a}P > 0.05$ indicates no significant difference between the study and control groups; $^{b}P < 0.05$ indicates that the difference between the study and control groups was statistically significant.

DISCUSSION

ASO typically arises as a comorbid condition in conjunction with the progression of atherosclerosis. Atherosclerosis induces hemodynamic abnormalities, increasing blood viscosity and consequent blood stasis, predisposing individuals to abnormal coagulation function. Thrombosis is more likely to develop in regions of vascular constriction throughout the body[14-16]. Resting pain is a predominant clinical manifestation of ASO, characterized by persistent limb pain during periods of rest. It is a primary clinical symptom of Fontaine grade III[17]. The onset of resting pain in patients with ASO signals a potential risk of impending ischemic necrosis in the affected area, necessitating preventive measures to avert necrosis resulting from severe ischemia. While some patients resort to medication for relief, primarily non-steroidal and opioid analgesics, their rapid efficacy is counteracted by the risk of dependency and various side effects, limiting their frequent use. TCM attributes the onset of ASO to vascular pathologies, particularly choroidal obstruction. Factors such as overexertion, emotional instability, and external influences can disrupt bodily fluid and blood flow, leading to meridian

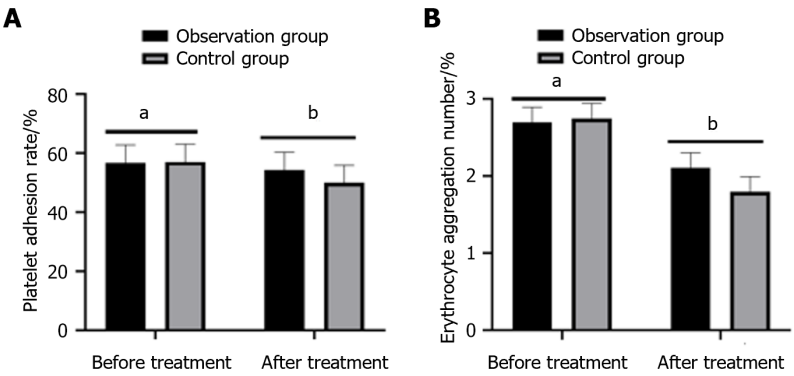

Figure 5 Comparison of hemorheological indicators between the two groups. A: Platelet adhesion rate; B: Erythrocyte aggregation number. [a]*P* > 0.05 indicates no significant difference between the study and control groups; [b]*P* < 0.05 indicates that the difference between the study and control groups was statistically significant.

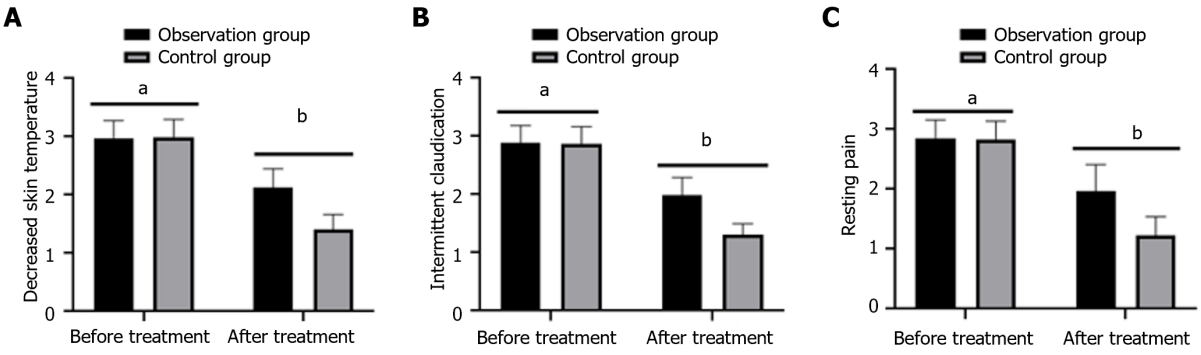

Figure 6 Comparison of traditional Chinese medicine symptom scores between the two groups. A: Skin temperature; B: Intermittent claudication; C: Resting pain. [a]*P* > 0.05 indicates no significant difference between the study and control groups; [b]*P* < 0.05 indicates that the difference between the study and control groups was statistically significant.

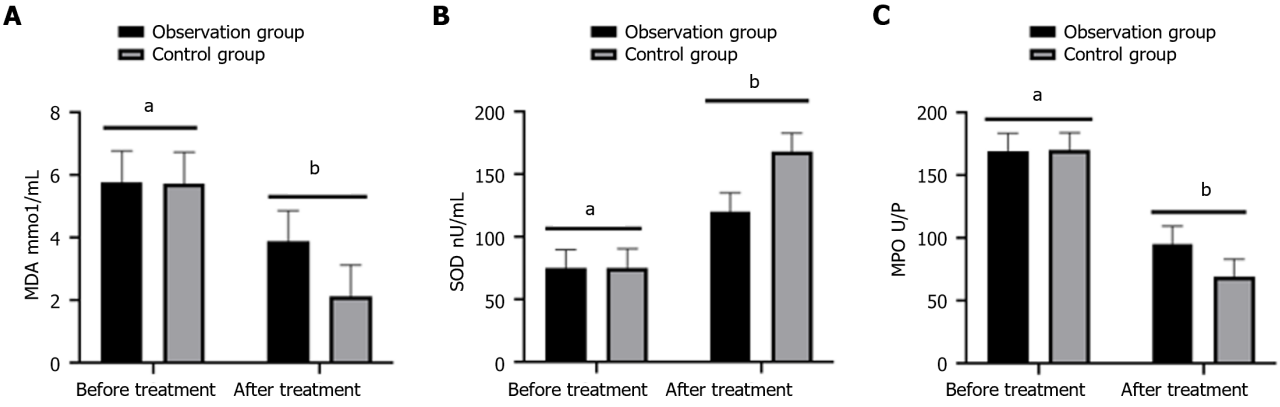

Figure 7 Oxidative stress indicators. A: Malondialdehyde (MDA); B: Superoxide dismutase (SOD); C: Myeloperoxidase (MPO). [a]*P* > 0.05 indicates no significant difference between the study and control groups; [b]*P* < 0.05 indicates that the difference between the study and control groups was statistically significant.

blockages caused by blood stasis, which impedes limb nourishment and precipitates ASO[18]. In the initial stages of treatment, attention should be placed on strategies such as warming the meridians, dispersing cold, detoxification, heat clearance, dampness removal, and collateral unblocking. In the later stages, attention should shift to processes such as kidney tonification, blood nourishment, promotion of blood circulation, and detoxification[19]. Acupuncture and moxibustion are primary TCM modalities for addressing surgical ailments, capable of extracting external and internal toxins. The embedding of ear point beans is a pivotal component of acupuncture and moxibustion therapy, known for its minimal toxicity and side effects, significant clinical efficacy, and straightforward application. This method is increasingly adopted in pain management for diverse conditions[20].

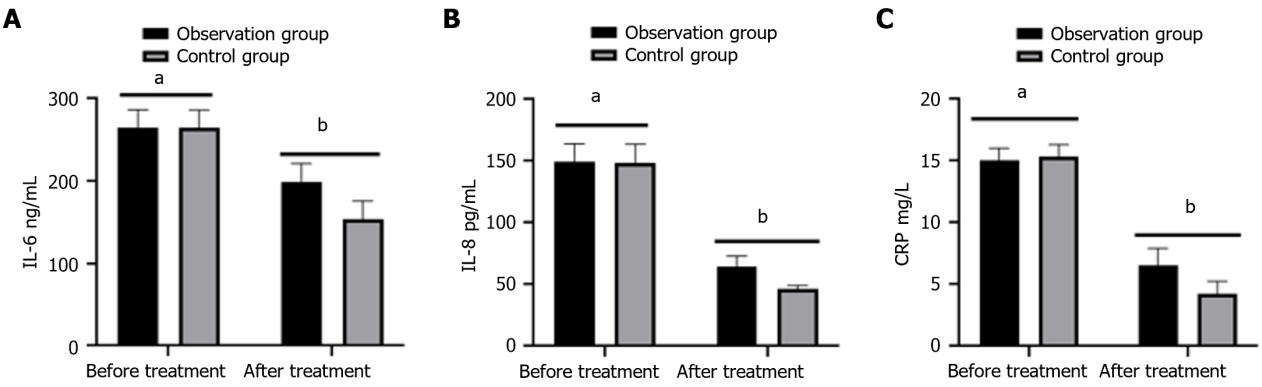

Figure 8 Inflammatory factor indicators. A: Interleukin (IL)-6; B: IL-8; C: C-reactive protein (CRP). [a]*P* > 0.05 indicates no significant difference between the study and control groups; [b]*P* < 0.05 indicates that the difference between the study and control groups was statistically significant.

The research results reveal a substantially superior total clinical efficacy in the study group compared to the control group, underscoring the favorable therapeutic outcomes associated with the combination of ear point embedding beans and Wenjing Sanhan prescription. The Wenjing Sanhan prescription, predominantly comprising Chinese medicinal materials such as *Aconite*, *Wulingzhi*, and *Safflower*, is prepared *via* water decoction, preserving the biological activity of the medicinal components and enhancing coagulation. Pharmacologically, *Safflower* contains potent compounds such as *Safflower* ketone and *Safflower* glycoside, which intervene in the coagulation cascade by inhibiting the synthesis, activation, and activity of coagulation factors and diminishing platelet aggregation, thereby regulating blood coagulation capacity. This mechanism stimulates endothelial cells to produce nitric oxide, facilitating vascular smooth muscle relaxation, vasodilation, enhanced blood flow, and improved circulation[21]. The ear acupoints hosting the embedded beans correspond to the body's meridians and organs, serving as reservoirs and sources of qi. By utilizing the inherent property of Wangbuliu seeds for continuous movement, the therapy aims to unblock meridians. Moreover, it employs acupuncture and moxibustion techniques, encompassing needle insertion, retention, movement, and initiation, to sustain a lasting and stable therapeutic effect[22]. This combination treatment significantly reduces platelet aggregation and improves the patient's symptoms.

The ankle-brachial artery pressure ratio primarily assesses ischemia severity in patients. The results of this study demonstrated a significantly higher ankle-brachial artery pressure ratio in the study group than in the control group, alongside significantly reduced hemorheological indicators such as whole blood viscosity, plasma viscosity, fibrinogen, platelet adhesion rate, and red blood cell aggregation index. This result indicates that the combination therapy of ear point embedding beans and warming meridians to dispel cold effectively enhances the ankle-brachial artery pressure ratio in patients with ASO and resting pain, alleviates limb ischemia, and reduces blood viscosity. This efficacy may be attributed to warming meridian and cold-dispersing formula components such as *Aconite*, which restores Yang and relieves adverse reactions; *Wulingzhi*, which breaks through blood and promotes blood circulation; *Puhuang*, which promotes blood circulation, hemostasis, and the resolution of blood stasis; Litchi seeds, which enhance qi circulation and disperse nodules; and *Wuyao*, which relieves qi stagnation and depression. The combined action of these ingredients effectively dispels cold and resolves blood stasis. Modern pharmacological studies have shown that aconite and *Wulingzhi* can mitigate blood hypercoagulability in patients by modulating pathways such as glucose and glycerophospholipid metabolism, inhibiting platelet aggregation, and exhibiting robust biological activity[23]. *Angelica sinensis* contains various compounds such as Rongben lactone and sodium ferulic acid, which possess the ability to decrease blood viscosity, enhance prothrombin time, lower plasma fibrinogen levels, shorten the electrophoresis time of platelets and red blood cells, and improve blood coagulation by inhibiting the synthesis of coagulation factors[24]. The Zhongshenmen point for embedding ear acupoints lies at the junction of the middle and lower thirds of the line between the pressure drop point and pelvic point. Acupuncture and moxibustion on this point exhibit significant sedative and analgesic effects. The Sympathetic point, positioned at the inner upper part of the inner third of the lower ear wheel, is one of the five blood-activating points. Acupuncture and moxibustion at this point can alleviate pain, relieve spasms, and regulate the contraction and relaxation of blood vessels. The hot acupoint at the midpoint of the line connecting the coccyx and abdomen is crucial for promoting blood circulation and unblocking meridians, thereby significantly enhancing peripheral blood circulation. The combined application of these points can dilate blood vessels, elevate the ankle-brachial artery pressure ratio, reduce blood viscosity, and ameliorate limb ischemia in patients[25].

Our comparison of TCM symptom scores between the two groups revealed significantly lower scores for skin temperature reduction, intermittent claudication, and resting pain in the study group following treatment compared to the control group. This finding indicates that combining ear acupoint embedding and warming meridians with a cold-dispersing formula alleviates skin temperature reduction, intermittent claudication, and resting pain in patients with ASO, yielding a favorable therapeutic outcome. The efficacy of this treatment stems from the components within the warming meridians and cold-dispersing formula: *Yujin* promotes qi circulation and relieves depression, cools blood, and breaks through blood stasis; *Myrrh* relieves pain and stimulates blood circulation; and *Xiangfu* soothes the liver, regulates qi, and relieves pain. The synergistic action of multiple drugs achieves the therapeutic goals of warming meridians, dispersing cold, removing dampness, unblocking collaterals, and reducing pain. Moreover, ginger-processed aconite regulates PGE2 and adrenaline, inducing thermal-related effects[26]. In the study by Dong *et al*[27], the Wenjing Sanhan

formula was employed to treat rheumatoid arthritis of the wind-cold dampness type, yielding significant analgesic effects consistent with the findings of this study. Treatment involving embedding beans in ear acupoints enhances peripheral blood circulation and elevates skin temperature by stimulating the patient's hot acupoints. The subcortical acupoint of the vascular system at the center of the buried bean ear acupoint is pivotal for regulating cerebral cortex function; it is positioned at the front and lower part of the inner side of the ear screen. Acupuncture can transmit nerve impulses to the brain, thereby influencing central function. This transmission enables the hypothalamus to modulate sympathetic and parasympathetic nerves to regulate the body's balance and nutritional status; it governs the hypothalamic-pituitary system, impacting the dynamic equilibrium of humoral hormones in the body, and triggers non-specific protective behaviors, improving immune factors to alleviate pain. The synergistic effect of this combination therapy yields favorable therapeutic outcomes.

Ear point embedding beans exert significant sedative and analgesic effects on the Shenmen point through acupuncture and moxibustion. Similarly, the Sympathetic point, one of the five blood-activating points, responds to acupuncture and moxibustion by relieving pain, easing spasms, and regulating blood vessel contraction and relaxation[24]. Ear point embedding beans combined with warming meridians and cold-dispersing formulas represent TCM therapies with targeted and comprehensive regulatory effects. The warming meridians and cold-dispersing formula effectively warm and unblock the meridians, promote the circulation of qi and blood, and improve the rheological properties of blood. The research results suggest that this combined approach of TCM and medication can effectively reduce oxidative stress levels in patients with ASO. The efficacy of these treatments stems from the abundance of active ingredients such as cinnamic acid and eugenol. These compounds act as scavengers for free radicals, engaging with them to reduce accumulation and damage. They provide electrons or hydrogen atoms, stabilizing free radicals and mitigating their damage to cells, thereby lowering oxidative stress levels. TCM theorizes that ear acupoints are interconnected with the body's meridians and organs, serving as reflex areas for the human nervous system. Stimulating these acupoints triggers a response in the nervous system, regulating the activity of the neuroendocrine system and consequently influencing oxidative stress. Furthermore, our results showed that the study groups exhibited lower inflammatory factor levels than the control group. This observation indicates that the combined approach of ear point embedding beans and warming meridians with a cold-dispersing formula reduces inflammatory factor levels in patients. This effect can be attributed to the active compounds such as quercetin and kaempferol in the Wenjing Sanhan formula, which possess potent anti-inflammatory properties. These compounds act on targets such as IL-6, influencing inflammatory and associated apoptotic pathways, thereby exerting anti-inflammatory effects[28]. Burying beans in specific ear acupoints stimulates nerve endings, influencing corresponding organs and systems. This method regulates immune system function through neural reflex mechanisms, diminishing inflammatory reactions and enhancing immunity. Combining these treatment methods improves inflammatory factor levels by regulating immune system function, and promoting blood and qi circulation. A study by scholars such as Lin *et al*[25] has shown that treating lower-limb ASO with warming yang, dispersing cold, and promoting blood circulation yielded a clinically effective rate of 93.33%, significantly inhibiting inflammatory factors, aligning with our study results.

CONCLUSION

In summary, combining ear point embedding beans and warming meridians with the cold-dispersing formula alleviates resting pain in patients with lower-limb ASO. This approach significantly increases the ankle-brachial artery pressure ratio, reduces hemorheological indicators, and improves TCM symptom scores. It demonstrates substantial clinical efficacy, and warrants further promotion and application in clinical settings. However, due to the limited number of cases in this study, future research should involve a larger sample size for more comprehensive investigations.

FOOTNOTES

Author contributions: Li J designed the research; Li YP performed the research and wrote the paper; Su T, Su ZH, and Xue XL contributed new reagents or analytic tools; Shi HR analyzed the data.

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ORIGINAL ARTICLE

Clinical and Translational Research

Computed tomography-based radiomics predicts the fibroblast-related gene *EZH2* expression level and survival of hepatocellular carcinoma

Ting-Yu Yu, Ze-Juan Zhan, Qi Lin, Zhen-Huan Huang

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is the most common subtype of liver cancer. The primary treatment strategies for HCC currently include liver transplantation and surgical resection. However, these methods often yield unsatisfactory outcomes, leading to a poor prognosis for many patients. This underscores the urgent need to identify and evaluate novel therapeutic targets that can improve the prognosis and survival rate of HCC patients.

AIM

To construct a radiomics model that can accurately predict the *EZH2* expression in HCC.

METHODS

Gene expression, clinical parameters, HCC-related radiomics, and fibroblast-related genes were acquired from public databases. A gene model was developed, and its clinical efficacy was assessed statistically. Drug sensitivity analysis was conducted with identified hub genes. Radiomics features were extracted and machine learning algorithms were employed to generate a radiomics model related to the hub genes. A nomogram was used to illustrate the prognostic significance of the computed Radscore and the hub genes in the context of HCC patient outcomes.

RESULTS

EZH2 and *NRAS* were independent predictors for prognosis of HCC and were utilized to construct a predictive gene model. This model demonstrated robust performance in diagnosing HCC and predicted an unfavorable prognosis. A

negative correlation was observed between *EZH2* expression and drug sensitivity. Elevated *EZH2* expression was linked to poorer prognosis, and its diagnostic value in HCC surpassed that of the risk model. A radiomics model, developed using a logistic algorithm, also showed superior efficiency in predicting *EZH2* expression. The Radscore was higher in the group with high *EZH2* expression. A nomogram was constructed to visually demonstrate the significant roles of the radiomics model and *EZH2* expression in predicting the overall survival of HCC patients.

CONCLUSION

EZH2 plays significant roles in diagnosing HCC and therapeutic efficacy. A radiomics model, developed using a logistic algorithm, efficiently predicted *EZH2* expression and exhibited strong correlation with HCC prognosis.

Key Words: Hepatocellular carcinoma; Fibroblast; *EZH2*; Radiomics model; Diagnosis; Prognosis

Core Tip: This study integrated radiomics molecular analysis based on computed tomography images. It aimed to identify important molecular biomarkers associated with hepatocellular carcinoma (HCC), particularly *EZH2*, and establish a radiomics model to predict *EZH2* expression and its association with the prognosis of HCC patients. The results of this study demonstrated a close correlation between the radiomics model, *EZH2* expression, and HCC patient prognosis, suggesting that a radiomics analysis can provide additional molecular information and offer a new approach to clinical treatment of HCC.

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INTRODUCTION

Liver cancer, a highly heterogeneous and malignant tumor associated with the digestive system, is the fourth-leading cause of cancer-related fatalities worldwide[1,2]. Hepatocellular carcinoma (HCC), the most common subtype of liver cancer, accounts for over 75% of all cases[3]. In China, HCC is responsible for the second-highest cancer mortality rate. This is due to various factors including historical, demographic, and health conditions[4]. Major contributors to the development of HCC include chronic infection with hepatitis B virus or hepatitis C virus, excessive alcohol consumption, and liver fibrosis[5]. Presently, the major treatment strategies for HCC are liver transplantation and surgical resection, but these methods often yield unsatisfactory outcomes[6]. This underscores the urgent need to identify novel therapeutic targets that can improve the prognosis and overall survival (OS) rate of HCC patients.

Persistent liver damage and fibrosis are significant risk factors for HCC development[7]. Research indicates that most HCC patients had preexisting cirrhosis, with approximately one-third of these cirrhosis patients eventually developing HCC[8]. Moreover, the tumor microenvironment (TME) has been shown to facilitate tumor progression[9]. In HCC, the interactions within the TME, composed of cancer-associated fibroblasts (CAFs), immune cells, endothelial cells, and HCC cells, significantly increase tumor proliferation, invasion, metastasis, and chemoresistance[9]. Additionally, CAFs, the primary component in TME stroma, have previously been shown to promote the aggressiveness of various cancers, including HCC[10,11].

Genetics plays a crucial role in understanding the structure and function of organisms and has been widely applied in various medical fields, including clinical diagnosis, drug development, and disease prediction. In this study, an enhancer of the *EZH2* subunit was identified as a key fibroblast-related gene (FRG) in HCC. Furthermore, *EZH2* demonstrated significant diagnostic value in HCC. As a core component of the polycomb repressive complex 2, *EZH2* is involved in the onset and progression of various cancers, including prostate, breast, melanoma, bladder, and endometrial[12]. In malignant tumors, *EZH2* suppresses the expression of numerous tumor suppressor genes, thereby facilitating carcinogenesis[13].

Radiomics, an emerging technological tool, transforms standard medical images into quantitative representations. By analyzing quantitative imaging features, radiomics has substantially lowered the cost of diagnosing diseases and the need for invasive surgeries[14]. Preoperative computed tomography (CT) radiomics is widely used for diagnosing, staging, and assessing the treatment efficacy in HCC, demonstrating robust evaluation and prediction capabilities[15].

In this study, FRGs were retrieved and used to develop a gene model associated with HCC prognosis through various bioinformatics analyses. The drug sensitivity analysis and molecular docking results highlighted the significant role of *EZH2* in treating HCC patients. Subsequently, leveraging CT images, this study aimed to establish a radiomics model for predicting *EZH2* expression levels, offering valuable insights for clinical HCC treatment.

MATERIALS AND METHODS

RNA-seq and CT imaging data collection

Figure 1 illustrates the research process undertaken in this study. RNA-seq data and clinicopathological information (age, sex, pathological stage, and grade) of HCC patients were retrieved from The Cancer Genome Atlas (TCGA) database (https://tcga-data.nci.nih.gov/tcga/). The samples without complete expression and clinical information in the TCGA-HCC dataset were excluded. Subsequently, HCC patient CT image data was downloaded from The Cancer Imaging Archive (TCIA) database (http://www.cancerimagingarchive.net). The TCIA data was carefully filtered to exclude any data that did not overlap with the TCGA data as well as CT images from tumor excision patients and those with poor image pixels. Ultimately, this study included 339 HCC tumor samples, 50 normal samples, and 41 imaging datasets. Notably, all tumor samples received radiation and pharmaceutical therapy. Additionally, the GSE25097 dataset, comprising 249 normal and 268 HCC samples, was retrieved from the Gene Expression Omnibus database, using the GPL10687 platform.

Acquisition and enrichment analysis of differentially expressed FRG in HCC

The GeneCard database (https://www.genecards.org/) was used to screen for FRGs, using the keyword "Fibroblast." Next, differentially expressed genes (DEGs) between normal and tumor tissues in the TCGA-HCC dataset were identified using the limma package in R language, with a threshold setting of $|\log2 (\text{Fold change})| > 2.0$ and $P < 0.05$. Finally, Venn diagram analysis was used to identify FRGs that are DEGs in HCC.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted on the FRGs differentially expressed in HCC, using the org.Hs.eg.db and clusterProfiler packages in R software. GO describes the function of all gene products in various organisms and identifies characteristic biological features of high-throughput genomes, including biological process, cellular component, and molecular function[16]. KEGG is a widely used database that stores information on genomes, biological pathways, diseases, and drugs.

Construction of a gene model

Firstly, least absolute shrinkage and selection operator regression analysis was performed on the differentially expressed FRGs using the glmnet package in R software to identify key genes associated with the OS of HCC patients from the TCGA dataset. Secondly, univariate and multivariate Cox regression analyses were conducted sequentially to identify genes significantly associated with HCC prognosis. Finally, based on the multivariate Cox regression analysis, an HCC prognostic gene model was established using the following formula: Risk score = gene $\exp_1 \times \beta_1$ + gene $\exp_2 \times \beta_2$ + ... + gene $\exp_n \times \beta_n$, where "gene exp" represents the expression level of the gene, and β represents the corresponding coefficient of the multivariate Cox regression.

Evaluation and validation of the gene model

The receiver operating characteristic (ROC) curve analysis was performed on the TCGA and GSE25097 HCC datasets using the R package pROC. This was to assess the diagnostic efficacy of the gene model. Kaplan-Meier analysis of the risk score and OS in the TCGA data was conducted using the survival package and visualized using the survminer package in R software. Additionally, R software generated a forest plot to determine the relationship between the gene risk score and HCC prognosis across different clinical feature groups. Multivariate Cox regression analysis was employed to verify the independent prognostic value of the risk score.

Drug sensitivity analysis and molecular docking

The Cancer Therapeutics Response Portal database contains data on the sensitivity of different tumor cells to various chemotherapy drugs. The database was used to calculate the sensitivity of genes to different chemotherapy drugs with the help of the oncoprdict package in R software. Then, the crystal structures of these genes were obtained from the Research Collaboratory for Structural Bioinformatics database (https://www.rcsb). The binding efficiency of genes with crucial chemotherapy drugs was analyzed using the Autodock software (Version 4.2.6). A binding energy l ≤ -1.5 kcal/mol indicates a good binding effect[17].

Extraction of radiomics features

The entire tumor region was manually delineated by two radiologists using 3D Slicer (Version 5.4.0) who also independently described the lesions without knowledge of the patient's clinical details. The pyradiomics package in Python software was used for radiomics feature extraction and data normalization. A total of 837 radiomics features were acquired, including first-order features, shape, and texture.

The intraclass correlation coefficient was calculated using the R "irr" package to evaluate the consistency of the extracted radiomics features based on the region of interest outlined by the two radiologists. Intraclass correlation coefficient values ≥ 0.75 indicated good consistency, 0.51-0.74 indicated moderate consistency, and ≤ 0.50 indicated poor consistency[18].

Selection of radiomics features

The TCIA image data related to HCC were divided into two groups based on the median expression level of *EZH2*. Radiomics features related to *EZH2* were selected using the XG Boost package in Python. Feature importance analysis was conducted using multiple machine learning algorithms to identify radiomics features closely associated with *EZH2*.

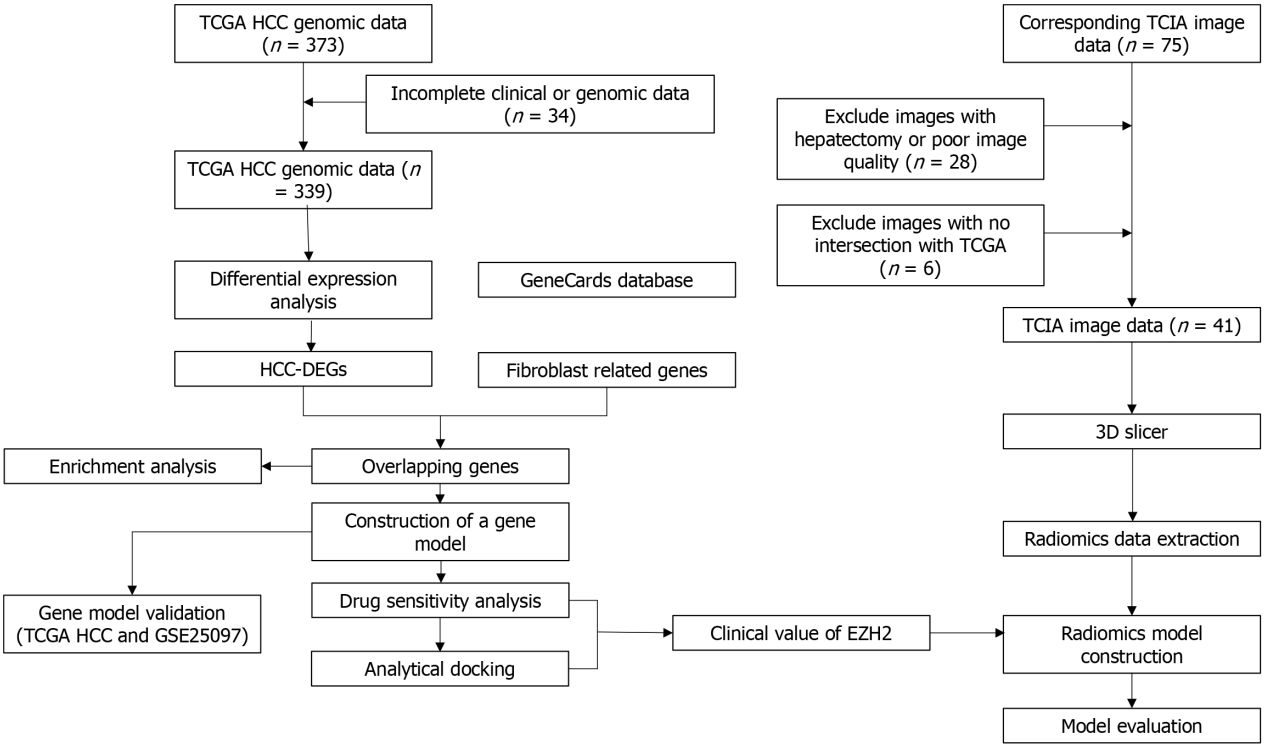

Figure 1 Entire analytical process of the study. DEGs: Differentially expressed genes; HCC: Hepatocellular carcinoma; TCGA: The Cancer Genome Atlas; TCIA: The Cancer Imaging Archive.

Construction and evaluation of the radiomics model

Two radiomics models related to *EZH2*, specifically logistic regression and random forest models, were constructed using multiple machine learning algorithms. A comprehensive multimodel analysis was conducted to determine the radiomics model with superior performance in predicting *EZH2*. Subsequently, a restricted cubic spline analysis was executed on the Radscore and *EZH2* using the rms package in R software to predict their nonlinear relationship. Ultimately, a nomogram was constructed to evaluate the correlation of *EZH2* and Radscore and the prognosis of HCC patients.

Statistical analysis

Data analysis and visualization were performed using R (Version 4.2.2) and Python (Version 3.6.6). Quantitative data was expressed as mean ± standard deviation, median, or quartile. The Student's *t*-test or Wilcoxon test was employed to analyze comparisons between groups. Categorical variables were represented as counts and percentages, and group comparisons were performed using the χ^2 test. The Delong test was used to compare the differences in area under the curve (AUC) values. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Identification and enrichment analysis of differentially expressed FRGs

Initially, 144247 FRGs were extracted from the GeneCards database, but this was narrowed down to 666 FRGs based on a threshold score ≥ 5. A differential analysis of the HCC data revealed 8205 DEGs between HCC and normal tissues, which included 7366 upregulated genes and 839 downregulated genes ($P < 0.05$, Figure 2A). A total of 299 FRGs were identified to be differentially expressed in HCC (Figure 2B).

The biological processes that differentially expressed FRGs are a part of were identified by enrichment analysis in GO. The analysis revealed that these genes were primarily a part of various stimuli response pathways, such as chemicals, organic substances, and stress. Some were also involved in cell proliferation (Figure 2C). KEGG enrichment analysis revealed that the differentially expressed FRGs were primarily associated with pathways known to play a role in cancer pathogenesis and survival, such as PI3K-Akt signaling pathway, proteoglycans in cancer, focal adhesion, hepatitis B, HCC, and hepatitis C alcoholism (Figure 2D). These pathways are closely related to the onset and development of tumors.

Construction of a gene model

To construct a gene model associated with HCC prognosis, a sequence of analyses was conducted, including least absolute shrinkage and selection operator regression analysis as well as univariate and multivariate Cox regression. Among the 299 differentially expressed FRGs, 7 genes were significantly associated with the OS of HCC patients

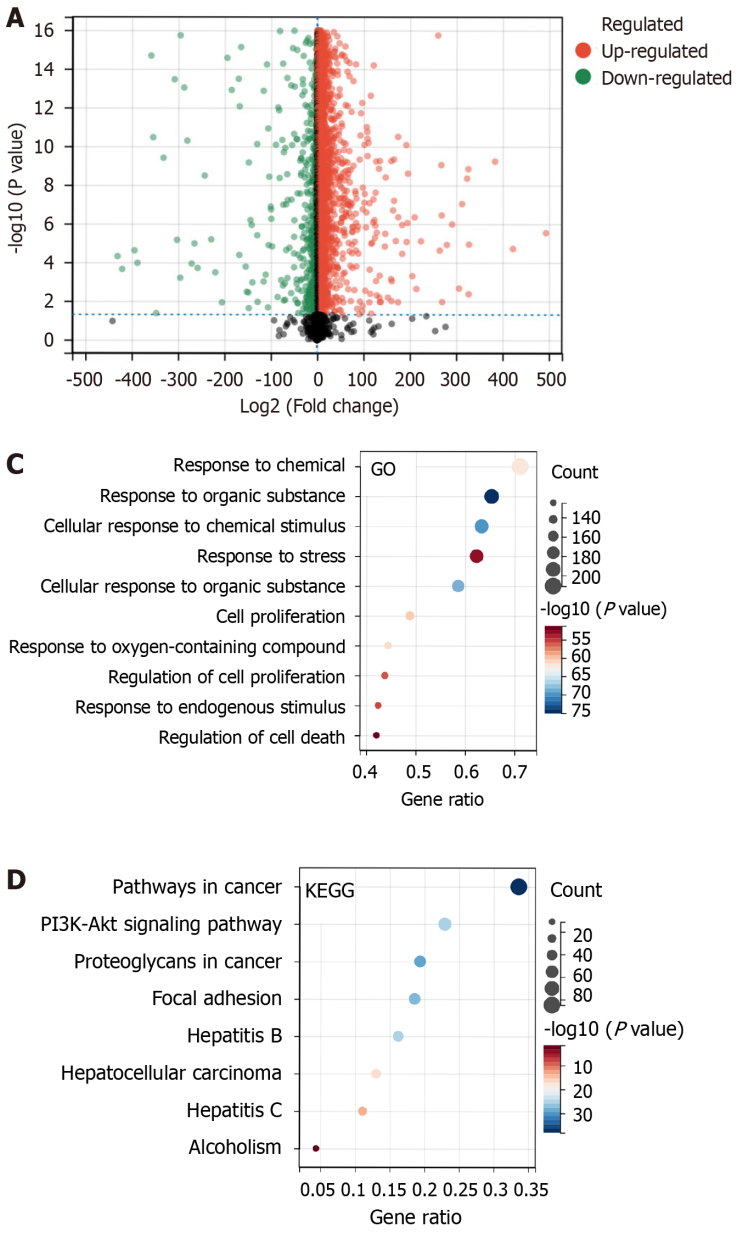

Figure 2 Identification and enrichment analysis of differentially expressed fibroblast-related genes. A: Volcano plot was used to visualize the results of differential analysis between normal and tumor tissues in hepatocellular carcinoma (HCC); B: Venn diagram of fibroblast-related genes (FRGs) and HCC-differentially expressed genes (DEGs); C: Gene ontology (GO) enrichment analyses of differentially expressed FRGs; D: Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of differentially expressed FRGs.

(Figure 3). Furthermore, *EZH2* and *NRAS* were found to independently predict the prognosis of HCC patients ($P < 0.05$, Table 1). The gene model was constructed based on the outcomes of the multivariate Cox regression analysis using the formula: Risk score = 0.083 × *EZH2* + 0.03 × *NRAS*.

Evaluation and validation of the gene model

The differential expression analysis of the risk score between the HCC and normal groups was conducted. Notably, significantly higher risk scores were observed in the HCC group in the TCGA and GSE25097 HCC datasets ($P < 0.05$, Figure 4A and B). Additionally, the risk score as a continuous and categorical variable was found to be independent of age, sex, grade, and pathological stage (S1 + S2; stage I and stage II; S3 + S4; stage III and stage IV) ($P > 0.05$, Table 2 and Figure 4C-F). Subsequently, ROC analysis was performed to explore the diagnostic efficiency of the gene model. In the TCGA-HCC and GSE25097 datasets, the gene model efficiently distinguished HCC from normal samples, with an AUC value of 0.94 and 0.95, respectively ($P < 0.05$) (Figure 4G and H). These results indicated that the risk model was highly effective in diagnosing HCC.

Prognostic value of the gene model

A Kaplan-Meier analysis was conducted to investigate the association of the risk score with HCC prognosis. As depicted in Figure 5A, a higher risk score indicates a poor prognosis for HCC patients. Additionally, among HCC patients aged ≤

Table 1 Correlation between key genes and prognosis of hepatocellular carcinoma patients

Characteristic	Total, *n*	Univariate analysis		Multivariate analysis	
		Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
ATIC	339	1.042 (1.027-1.058)	< 0.001	1.011 (0.989-1.033)	0.348
EZH2	339	1.196 (1.128-1.269)	< 0.001	1.087 (1.006-1.174)	0.035
HDGF	339	1.010 (1.006-1.014)	< 0.001	1.004 (0.999-1.026)	0.104
HEXB	339	1.027 (1.014-1.039)	< 0.001	1.013 (0.999-1.026)	0.060
HSPA4	339	1.040 (1.023-1.058)	< 0.001	1.017 (0.996-1.039)	0.117
NRAS	339	1.066 (1.042-1.091)	< 0.001	1.031 (1.003-1.059)	0.032
PPT1	339	1.030 (1.019-1.041)	< 0.001	1.004 (0.988-1.020)	0.665

CI: Confidence interval.

Table 2 Relationship between risk score and clinicopathological parameters in hepatocellular carcinoma patients

Variables	Total, *n* = 339	Risk score-low, *n* = 170	Risk score-high, *n* = 169	*P* value
Age	61.000 (51.000, 68.000)	62.000 (52.000, 69.000)	59.000 (51.000, 67.000)	0.083
Sex				0.310
Female	107 (31.6%)	58 (34.1%)	49 (29.0%)	
Male	232 (68.4%)	112 (65.9%)	112 (71.0%)	
Stage				0.876
S1+S2	252 (74.3%)	127 (74.7%)	125 (74.0%)	
S3+S4	87 (25.7%)	43 (25.3%)	44 (26.0%)	
Grade				0.457
G1+G2	212 (62.5%)	103 (60.6%)	109 (64.5%)	
G3+G4	127 (35.5%)	67 (39.4%)	60 (35.5%)	

S1 + S2: Stage I and stage II; S3 + S4: Stage III and stage IV.

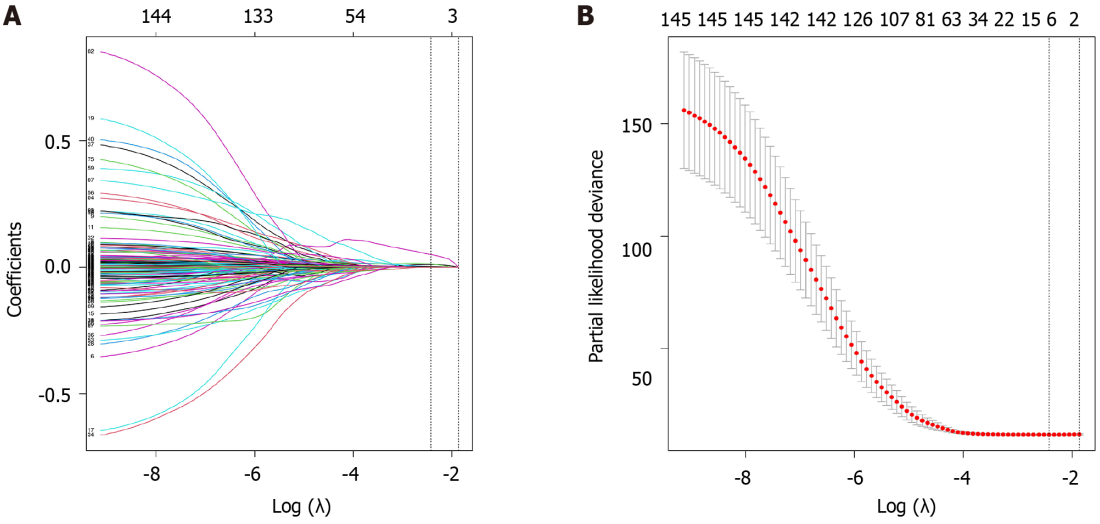

Figure 3 Selection of hub genes related to hepatocellular carcinoma prognosis. A: Least absolute shrinkage and selection operator (LASSO) correlation coefficient change curve; B: LASSO cross-validation curve.

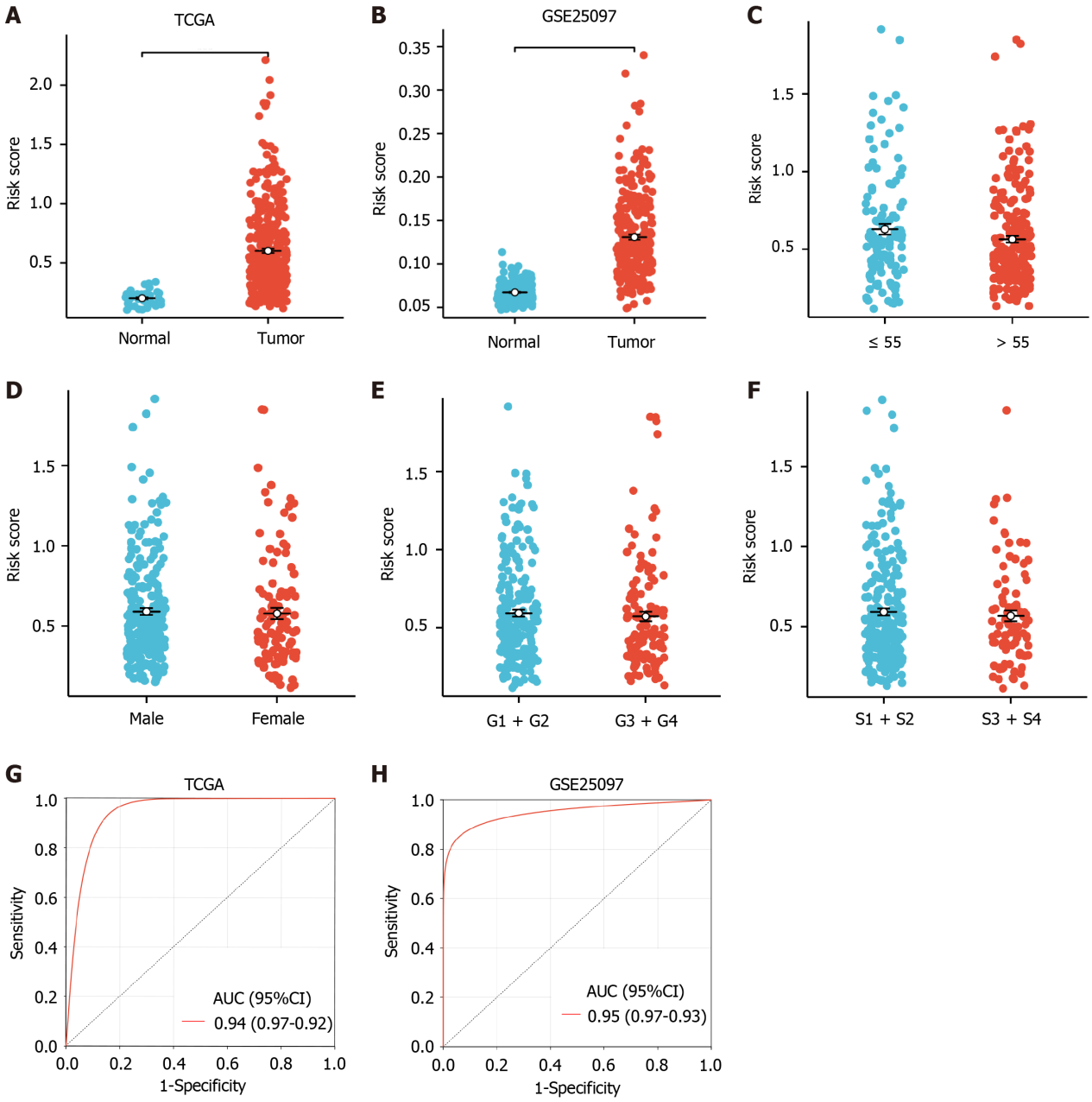

Figure 4 Evaluation and validation of risk model. A and B: Based on the Cancer Genome Atlas (TCGA)-Hepatocellular carcinoma (HCC) and GSE25097 datasets, the risk score was higher in the HCC samples; C: Relationship of risk score with age; D: Relationship of risk score with sex; E: Relationship of risk score with grade; F: Relationship of risk score with pathological stage; G: Receiver operating characteristic (ROC) curve of the risk score in the TCGA-HCC; H: ROC curve of the risk score in the GSE25097 datasets for distinguishing HCC and normal samples. S1 + S2: Stage I and stage II; S3 + S4: Stage III and stage IV. AUC: Area under the curve; CI: Confidence interval.

55 [hazard ratio (HR) = 4.46 (2.32-8.58), $P < 0.05$] and > 55 [HR = 2.55 (1.60-4.07), $P < 0.05$], female [HR = 2.97 (1.25-7.08), $P < 0.05$] and male [HR = 3.03 (1.89-4.85), $P < 0.05$], G1 + G2 [HR = 2.13 (1.36-3.35), $P < 0.05$] and G3 + G4 [HR = 4.15 (2.13-8.09), $P < 0.05$], and S1 + S2 [HR = 3.01 (1.94-4.66), $P < 0.05$] and S3 + S4 [HR = 3.62 (1.63-8.05), $P < 0.05$], high-risk scores were associated with poorer prognosis (Figure 5B). These results indicated that higher risk scores were significantly related to unfavorable prognosis regardless of age, sex, grade, and stage. Furthermore, when age, sex, grade, pathological stage, and risk score were analyzed using a multivariate Cox regression analysis, the results showed that the risk score independently predicted poor prognosis in HCC patients ($P < 0.05$) (Table 3).

Drug sensitivity analysis and molecular docking

The goal was to investigate the therapeutic significance of specific genes within the gene model and identify potential therapeutic targets. To achieve this, the correlation between the expression levels of two genes, *EZH2* and *NRAS*, and the sensitivity of commonly used chemotherapy and targeted drugs were examined. Leveraging data from the Cancer Therapeutics Response Portal database, it was found that EZH2 expression was significantly negatively correlated with drug sensitivity (Figure 6A). Subsequently, four drugs, belinostat, BRD-K34222889, ciclopirox, and cytarabine hydrochloride, were selected for molecular docking analysis. Remarkably, EZH2 exhibited favorable interactions with

Table 3 Correlation between risk scores in clinical features and hepatocellular carcinoma prognosis

Characteristic	Total, *n*	Multivariate analysis	
		Hazard ratio (95%CI)	*P* value
Risk score	339	5.339 (3.139-9.078)	< 0.001
Age	339	1.018 (1.002-1.034)	0.028
Sex	339	1.010 (1.006-1.014)	0.172
Grade	339	1.113 (0.744-1.664)	0.603
Stage	339	0.888 (0.579-1.363)	0.588

CI: Confidence interval.

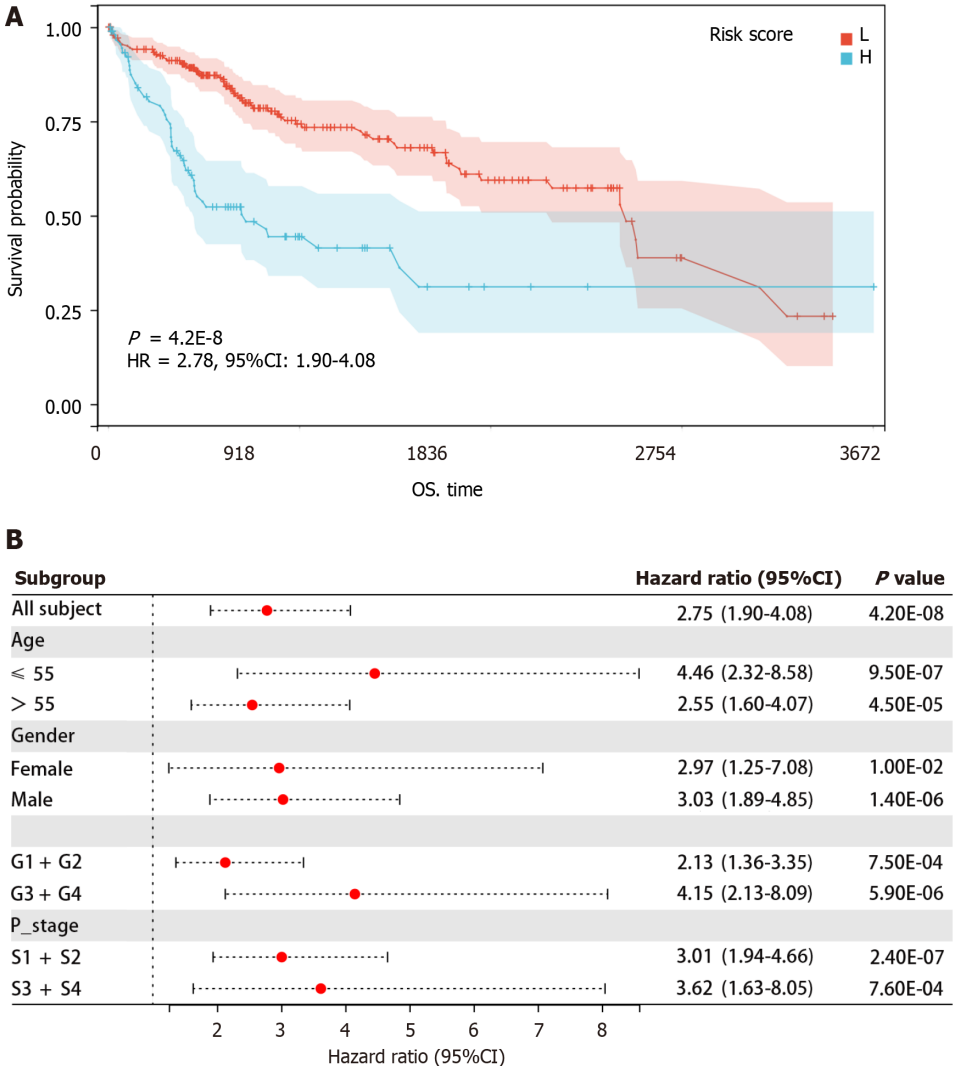

Figure 5 Prognostic model of the risk model. A: Kaplan-Meier curve showed that a higher risk score was associated with poor prognosis; B: Correlation between risk scores in clinical features and hepatocellular carcinoma prognosis. S1 + S2: Stage I and stage II; S3 + S4: Stage III and stage IV. CI: Confidence interval; H: High; HR: Hazard ratio; L: Low; OS: Overall survival.

these drugs (Table 4). The most promising docking outcomes were visualized using the PyMOL software ($P < 0.05$, Figure 6B). These findings underscored the potential of EZH2 as a therapeutic target for HCC, prompting further investigation of its value in HCC treatment.

Clinical value of EZH2 in HCC

The EZH2 protein levels were significantly higher in the HCC group compared to the normal group ($P < 0.05$, Figure 7A). Interestingly, patients with EZH2 overexpression had significantly shorter survival ($P < 0.05$, Figure 7B). Furthermore,

Table 4 Binding energy between EZH2 and four chemotherapy drugs in molecular docking

Medicine	Hub targets (PDB ID)	Binding energy in kcal/mol
Belinostat	EZH2 (5h14)	-4.58
BRD-K34222889	EZH2 (5h14)	-4.23
Ciclopirox	EZH2 (5h14)	-4.07
Cytarabine hydrochloride	EZH2 (5h14)	-1.75

PDB ID: Protein database ID.

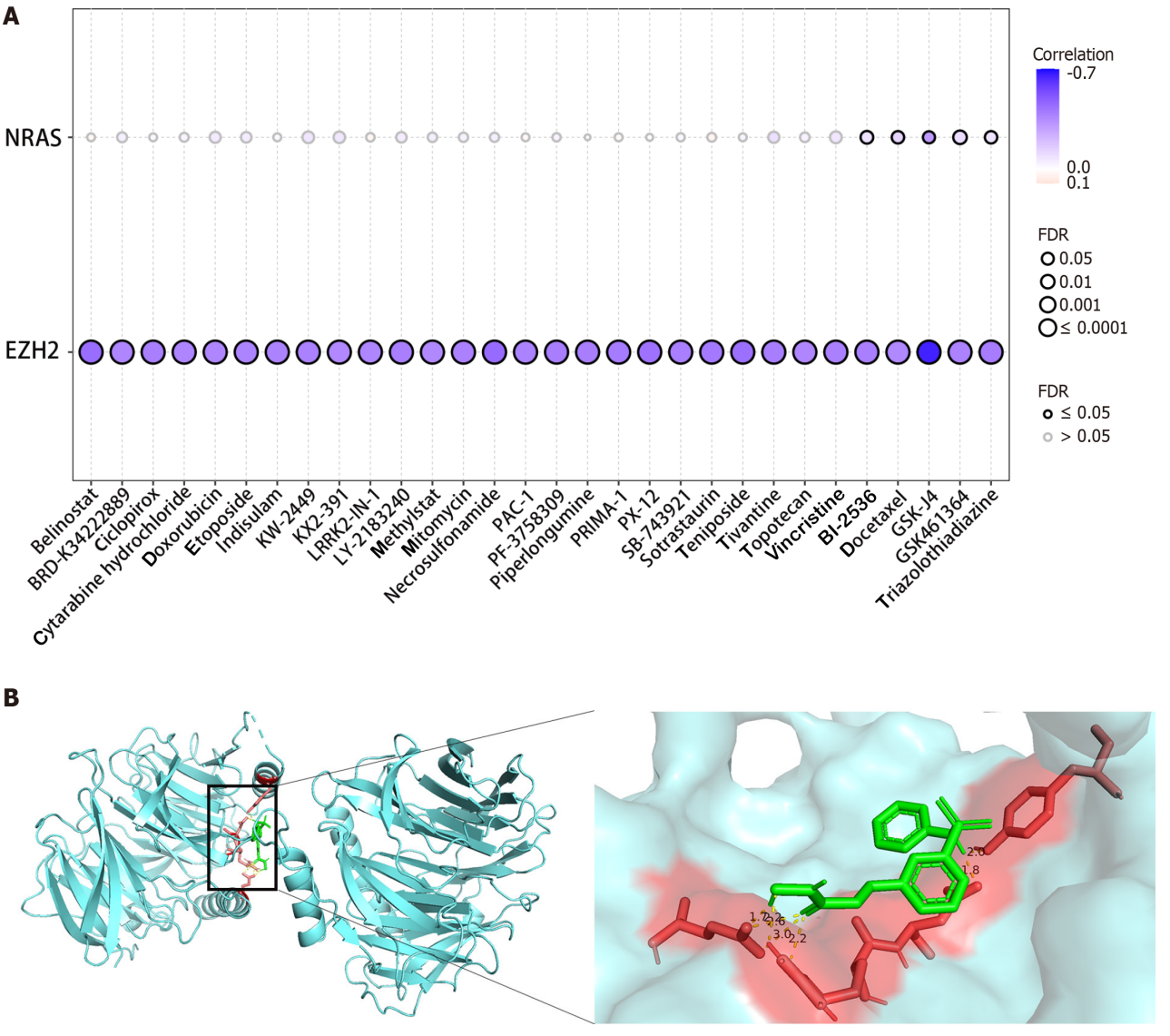

Figure 6 Drug sensitivity analysis and molecular docking. A: Correlation of EZH2 and NRAS with chemotherapy and cancer drugs; B: Molecular docking between EZH2 and belinostat. FDR: False discovery rate.

using the ROC analysis with AUC values, it was shown that EZH2 outperformed NRAS and the risk score in predicting HCC, achieving the highest AUC value of 0.978 ($P < 0.05$, Figure 7C and Table 5). The clinical efficacy of EZH2, NRAS, and the risk score was compared using the decision curve analysis (Figure 7D). These results confirmed the significance of *EZH2* in HCC and its potential as a diagnostic marker.

Screening of radiomics features related to EZH2 and radiomics model construction

The XGBoost-RFE algorithm was used to screen the radiomics features related to *EZH2*. The six features included original_glrlm_LongRunLowGrayLevelEmphasis, original_glrlm-SizeZoneNonUniformityNormalized, wavelet-LHL_glcm-DifferenceAverage, wavelet-LHL_glcm-Imc2, wavelet-LHL_firstorder- Maximum, and wavelet-LHL_glrlm-

Table 5 Difference in the area under the curves of *EZH2*, *NRAS*, and the risk score in diagnosing hepatocellular carcinoma

Name	*EZH2*	*NRAS*	Risk score
EZH2	/	< 0.05	< 0.05
NRAS	< 0.05	/	< 0.05
Risk score	< 0.05	< 0.05	/

/: Not applicable.

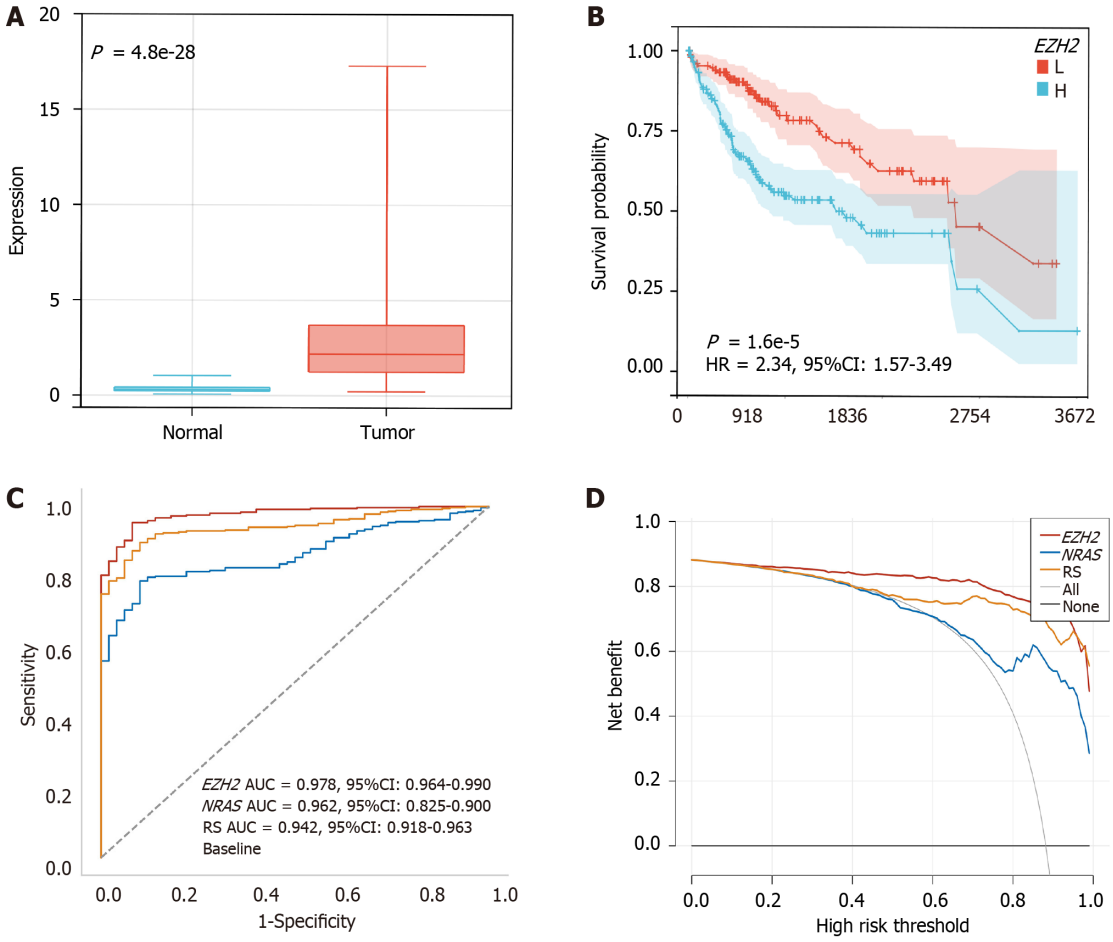

Figure 7 Clinical value of EZH2 in hepatocellular carcinoma. A: Expression of EZH2 in hepatocellular carcinoma (HCC) and normal groups; B: High (H) levels of EZH2 were associated with poor HCC prognosis; C: Receiver operating characteristic curve of EZH2, NARS, and risk score (RS) in diagnosing HCC; D: Decision curve analysis of EZH2, NRAS, and RS in diagnosing HCC. AUC: Area under the curve; CI: Confidence interval; HR: Hazard ratio; L: Low.

LongRunLowGrayLevelEmphasis. Both logistic and random forest algorithms were used to assess feature importance. Notably, original_glrlm- LongRunLowGrayLevelEmphasis and wavelet-LHL_glrlm-LongRunLowGrayLevelEmphasis were closely related to *EZH2* (Figure 8). Based on these findings, we selected original_glrlm- LongRunLowGrayLevelEmphasis and wavelet-LHL_glrlm-LongRunLowGrayLevelEmphasis to construct the *EZH2* prediction-related radiomics model. These steps ensured a comprehensive understanding of the *EZH2* radiomics signature and its potential implications for HCC prediction.

Evaluation of the radiomics model

A comprehensive multimodel analysis was conducted to construct the optimal radiomics model for predicting *EZH2*. The results revealed that the model built using the logistic algorithm not only exhibited better prediction capabilities but also demonstrated greater stability (Table 6 and Figure 9). Consequently, the Radscore was calculated based on the logistic algorithm as follows: Radscore = 0.095 × original_glrlm- LongRunLowGrayLevelEmphasis + 0.671 × wavelet-LHL_glrlm-LongRunLowGrayLevelEmphasis. This approach ensured a robust and accurate prediction of *EZH2* status using radiomics features.

Table 6 Results of predicting *EZH2* in the training set and validation set based on the logistic and random forest classifier algorithm

Classification model		AUC	Accuracy	Sensitivity	Specificity	F1 score
Validation	Logistic	0.792	0.667	0.800	0.833	0.833
	Random Forest	0.812	0.750	1.000	0.750	0.833
Training	Logistic	0.787	0.750	0.679	0.881	0.744
	Random Forest	1.000	0.938	1.000	1.000	1.000

AUC: Area under the curve.

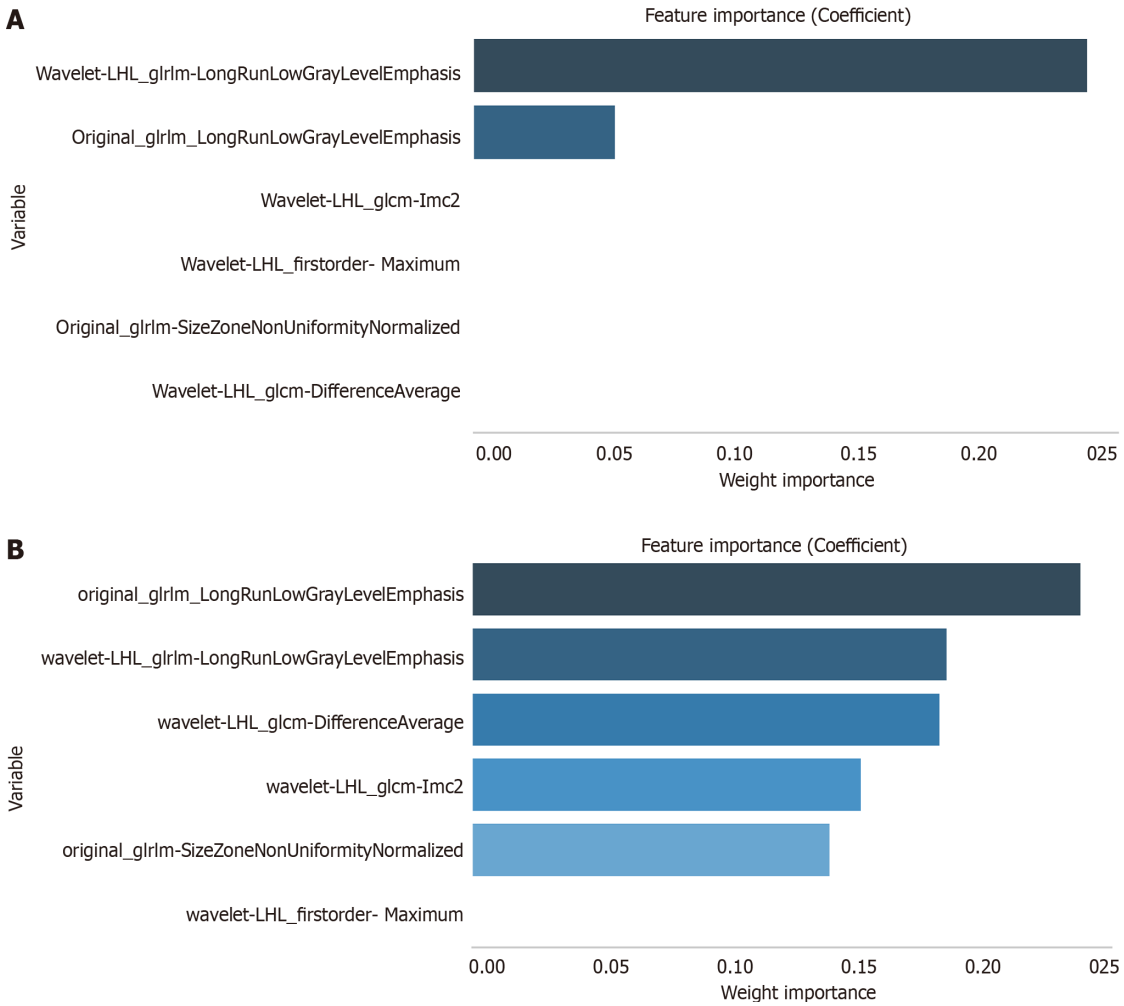

Figure 8 Screening of radiomics features related to *EZH2* and radiomics model construction. A: Feature importance based on the logistic algorithm; B: Feature importance based on the random forest algorithm.

Clinical value of the logistic algorithm-radiomics model

The restricted cubic spline revealed a linear relationship between *EZH2* and Radscore (Figure 10A). Specifically, the Radscore was higher in the *EZH2* high expression group than in the *EZH2* low expression group (Figure 10B). Moreover, the Radscore and *EZH2* played a crucial role in predicting the OS of HCC patients (Figure 10C). These findings emphasized the significance of *EZH2* and its association with patient outcomes in HCC.

DISCUSSION

This study combined radiomics and molecular analyses based on CT images to identify important molecular biomarkers associated with HCC, particularly *EZH2*. The study also aimed to establish a radiomics model that can predict *EZH2* expression and determine its association with HCC prognosis. Consequently, a significant correlation was observed

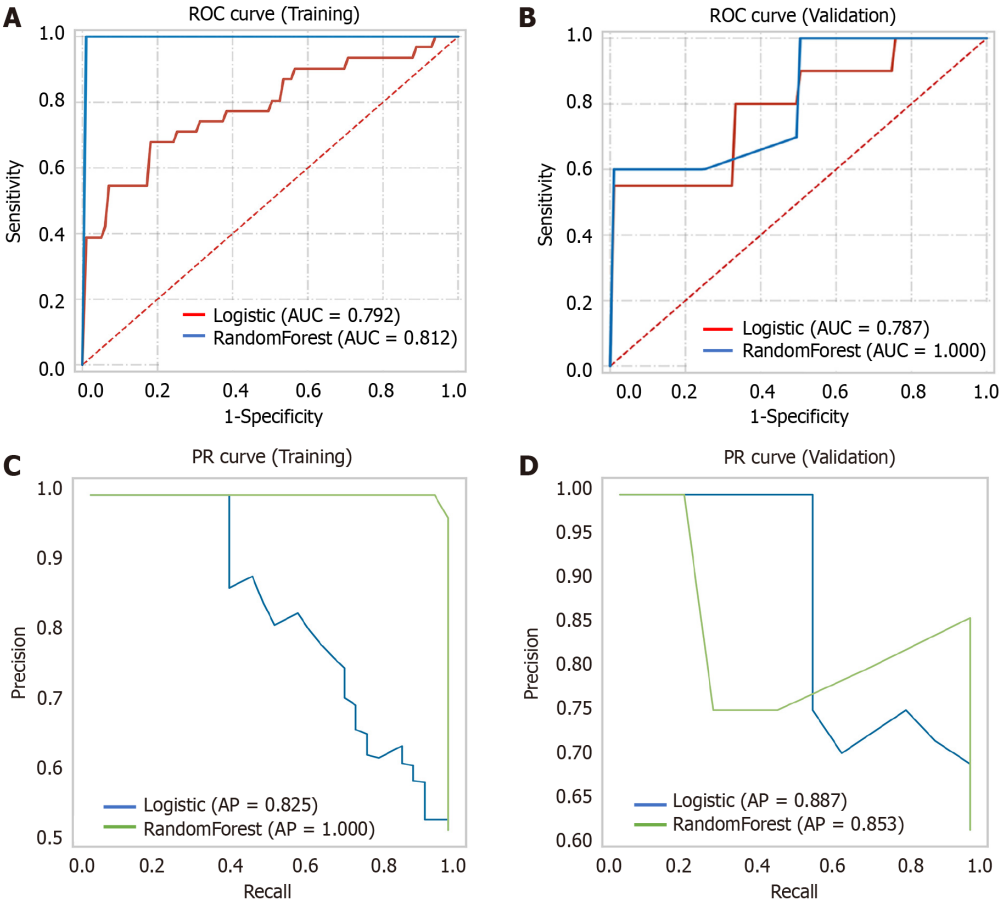

Figure 9 Results of predicting *EZH2* in the training set and validation set based on the logistic and random forest classifier algorithm. A: Receiver operating characteristic (ROC) curve in the training sets based on the logistic and random forest classifier algorithm; B: ROC curve in the validation sets based on the logistic and random forest classifier algorithm; C: Precision (PR) curve in the training sets based on the logistic and random forest classifier algorithm; D: PR curve in the validation sets based on the logistic and random forest classifier algorithm. AP: Average precision; AUC: Area under the curve.

between the radiomics model, *EZH2* expression, and HCC patient prognosis. This finding suggests that radiomics analysis can provide additional molecular information and offer a new approach to the clinical treatment of HCC.

The incidence rate of HCC is increasing globally, and it is generally associated with poor prognosis. Increasing evidence suggests that crosstalk between tumor cells, including HCC, and stromal cells promotes tumor progression[19]. Additionally, CAFs are the predominant stromal cells in the TME of HCC[20]. Liver cirrhosis with a significant number of activated fibroblasts typically predates HCC[21]. Venn diagram analysis identified 299 differentially expressed FRGs in HCC, which are primarily involved in biological processes related to stimuli response pathways including chemical, organic substance, and stress. These pathways are known to participate in tumor development. Through multiple analyses, we established a risk model related to the prognosis of HCC patients composed of two genes, *EZH2* and *NRAS*.

Drug sensitivity analysis revealed a significant negative correlation between *EZH2* and select chemotherapeutic and targeted drugs, while *NRAS* showed no significant correlation. Molecular docking results showed that the EZH2 (5h14) protein exhibited the strongest binding affinity with the small molecule ligand, belinostat, with a binding energy of -4.58 kcal/mol. In studies with human acute early granulocytic leukemia cells, belinostat independently depleted the histone EZH2, leading to the modification of H3 and H4 histones and ultimately achieving therapeutic effects[22]. This suggests that EZH2 may be a potential therapeutic target for HCC, and belinostat may exert its therapeutic effect by reducing EZH2 expression levels in HCC.

Further analysis revealed a significant association between *EZH2* expression and poor prognosis in HCC patients. *EZH2* also displayed significant HCC diagnostic capabilities. Therefore, *EZH2* was selected as the primary gene for subsequent analysis. Previous studies have shown that *EZH2* plays an important role in cell lineage determination and related signaling pathways, serving as a major regulator of DNA damage repair, autophagy, cell cycle progression, and cell senescence suppression[23]. The oncogenic mechanism of *EZH2* is primarily by suppressing the expression of tumor suppressor genes in cancer cells[24].

In gliomas, EZH2 can suppress the differentiation of astrocytes by inhibiting the expression of BMPR1B, resulting in increased tumorigenicity in gliomas[25]. EZH2 also promotes cancer metastasis by silencing E-cadherin and inducing epithelial-mesenchymal transition[26]. In scar research, RUNX3 mediates the proliferation of fibroblasts by deacetylating EZH2 through SIRT1[27]. In pulmonary fibrosis research, EZH2 negatively regulates autophagy in the fibrosis through the lncAPE-ELAVL1 complex[28]. Additionally, CAFs can promote angiogenesis through the VEGF-mediated EZH2 pathway, and overexpression of EZH2 is strongly associated with tumor invasion and reduced survival in liver cancer

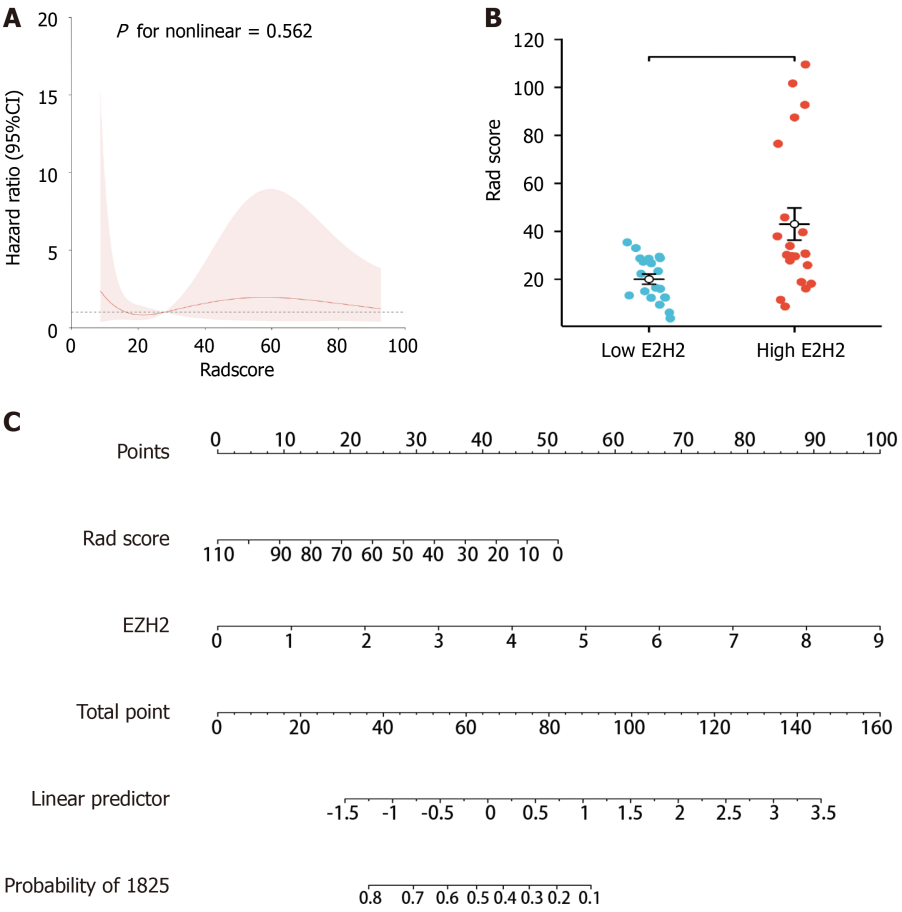

Figure 10 Clinical value of the radiomics model. A: Linear association of *EZH2* and radiomics model; B: Higher Radscore in the high *EZH2* expression group; C: Value of the rad score and *EZH2* in predicting hepatocellular carcinoma prognosis.

patients[29-31]. In conclusion, EZH2 is not only important for fibroblasts but also plays a significant role in tumor initiation and progression. This is consistent with the results of this study, which found a significant correlation between high *EZH2* expression and poor prognosis in HCC patients.

Radiomics is typically used for diagnosis and postoperative treatment efficacy assessment in HCC[14]. Using the data from preoperative liver-enhanced CT, Feng *et al*[32] constructed a radiomics model to predict the macro trabecular-massive subtype of HCC. Additionally, Xia *et al*[33] were able to predict microvascular invasion in HCC using extracted radiomics features from the preoperative registration or subtraction CT images. This study innovatively linked the radiomics features with *EZH2* expression to use *EZH2* expression to predict the OS of HCC patients from CT image data. A radiomics model related to *EZH2* expression was constructed, and the radiomics features included original_glrlm-LongRunLowGrayLevelEmphasis and wavelet-LHL_glrlm-LongRunLowGrayLevelEmphasis. Gray-Level Run-Length Matrix quantifies gray-level runs, defined as consecutive pixels with the same gray level value[34]. LongRunLowGray-LevelEmphasis is one of the 16 features of Gray-Level Run-Length Matrix, which is a measure of image texture, specifically the roughness. In tendinopathy imaging studies, GLLM-LongRunLowGrayLevelEmphasis can determine tissue changes longitudinally[35]. The higher the value, the rougher the texture. Aside from analyzing the distribution of the gray level of an image, it can also extract representative texture features[31]. In this study, the Radscore was higher in the *EZH2* high expression group, and the radiomics model was efficient in predicting *EZH2* in HCC. The nomogram demonstrated the importance of the Radscore and *EZH2* in predicting the OS of HCC patients. Thus, the radiomics model infers an association with *EZH2* and correlates with the prognosis of HCC patients.

This study leverages advanced imaging and bioinformatics tools to bridge the gap between macroscopic imaging features and microscopic genetic alterations. However, the radiomics and genomics data were obtained from public databases. Additionally, the scarcity of information on the CT images of HCC patients in the TCIA database made it impossible to divide the data into training and validation sets. Lastly, the analytical methods employed in the study primarily consisted of bioinformatics and statistics, lacking relevant experimental validation.

CONCLUSION

In conclusion, the gene model developed in this study, specifically related to fibroblasts in HCC, exhibited a strong association with HCC prognosis. Furthermore, the study identified *EZH2* as a potential therapeutic target linked to the

prognosis of HCC patients. Additionally, a radiomics model associated with *EZH2* can predict *EZH2* expression using CT features, which contributes to the diagnosis and treatment of HCC patients. By combining radiomics with molecular profiling in HCC, this study opens up new avenues for personalized and more effective treatment strategies.

FOOTNOTES

Author contributions: Yu TY and Zhan ZJ contributed to the conception and design; Yu TY, Lin Q, and Huang ZH contributed to the collection and assembly of data; Zhan ZJ and Huang ZH analyzed and interpreted the data; All authors wrote and approved the final manuscript.

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CASE REPORT

Endometrial carcinoma with cervical stromal invasion: Three case reports

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Abstract

BACKGROUND

Endometrial cancer is a kind of well-known tumors of female genitourinary system. Cervical stromal invasion is an adverse factor for poor prognosis of endometrial cancer. There is still controversy regarding the use of magnetic resonance imaging (MRI) in the diagnosis of cervical stromal invasion of endometrial cancer. The diagnosis of cervical stromal invasion varies significantly between different observers and institutions. We present a limited case series of the particular pattern of endometrial cancer, which infiltrates the cervical stroma and is often overlooked.

CASE SUMMARY

We present three cases of endometrial carcinoma with cervical stromal invasion with cancer-free uterine cavity. One patient, a reproductive-aged woman, exhibited irregular menstruation and was diagnosed with endometrial polyps by hysteroscopy and segmental curettage. A MRI scan revealed polypoid nodules within the internal cervical orifice. The other two cases were postmenopausal women who presented with abnormal vaginal bleeding. Hysteroscopy and segmental curettage suggested atypical hyperplasia of the endometrium. MRI scans did not detect any malignant signs in the endometrium. In one case, a non-thickened endometrium was observed, while in another, hyperplasia of the endometrium was seen. Notably, none of these patients had malignant tumors identified in the uterine cavity *via* MRI scans. However, postoperative pathological results following hysterectomy consistently indicated cervical stromal invasion.

CONCLUSION
Cervical stromal invasion is easily missed if no cancer is found in the uterine body on MRI. Immunohistochemistry of endoscopic curettage specimens should be conducted to avoid underestimation of the disease.

Key Words: Endometrial carcinoma; Cervical stromal invasion; Atypical hyperplasia of the endometrium; Magnetic resonance imaging; Case report

Core Tip: We focus on endometrial carcinoma with cervical stromal invasion, given its correlation with reduced 5-year survival rates and heightened lymph node metastasis risk in patients diagnosed with endometrial cancer. Patients with cervical stromal invasion are required to have a total hysterectomy and lymphadenectomy. In contrast, they only require a total hysterectomy. In instances of endometrial carcinoma that involves the cervix but lacks an apparent primary uterine body tumor, magnetic resonance imaging examinations should be performed with greater caution to prevent potential misdiagnoses.

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INTRODUCTION

Endometrial cancer is known as a malignant tumor, and predominantly occurs women aged over 50 years, with a proportion of cases (4%) occurring in individuals under 40 years[1]. Magnetic resonance imaging (MRI) is important for preoperative evaluation of endometrial cancer, which can accurately evaluate prognostic indicators, and this information can aid clinicians in devising tailored treatment strategies[2,3]. The discovery of cervical stromal invasion by MRI may have many challenges, including difficulty in identifying the boundary between cervix and uterine body, and difficulty in distinguishing between cervical stroma and mucosa infiltration[4]. Nonetheless, an accurate evaluation of cervical stromal involvement is crucial for determining accurate staging, prognosis, and the necessity for adjuvant therapy. We report the results in the context of clinical practice that endometrial cancer involving cervical stroma without obvious lesions in the uterine cavity, and highlight what contribution this study adds to the literature already existing on the topic and to future study perspectives.

CASE PRESENTATION

Chief complaints

Case 1: A 48-year-old female patient had been experiencing intermittent vaginal bleeding for five years.

Case 2: A 44-year-old female patient experienced irregular menstruation for one year.

Case 3: A 64-year-old female patient had persistent abnormal vaginal bleeding for 10 days.

History of present illness

Case 1: Six years after menopause, the patient experienced five years of intermittent vaginal bleeding without abdominal pain and fever. Ultrasound examination indicated a thickened endometrium.

Case 2: This patient of childbearing age, with regular menstruation, and no dysmenorrhea, in the previous year, her period was advanced by seven days, with a large amount of blood accompanied by clots.

Case 3: This patient who had been postmenopausal for 20 years, presented with vaginal bleeding that was initially observed eight years previously and had not been treated. The vaginal bleeding recurred ten days ago.

History of past illness

Case 1 and 2: No previous health conditions.

Case 3: This patient had a 1 year history of diabetes, and used 6-9 U subcutaneous insulin and took 0.5 g metformin orally three times daily. The fasting blood glucose was controlled at 6.1-6.9 mmol/L.

Personal and family history

All three patients did not have a history of smoking or alcohol abuse. They were no family history of the disease.

Physical examination

The vulva in these patients was normal. The vaginal mucosa exhibited smoothness, and the surface of the cervical region was also smooth. No masses were palpated in the pelvis, and no tenderness was detected within the pelvic cavity.

Laboratory examinations

Human papilloma virus, thinprep cytologic test were normal in all patients.

Imaging examinations

Case 1: Ultrasonography revealed that the endometrium was approximately 1.0 cm thick. Hysteroscopy indicated atypical hyperplasia of the endometrium. MRI (Figure 1) demonstrated an endometrium of similar thickness, with slightly elevated signals in both T2-weighted imaging (T2WI) (Figure 1A) and diffusion weighted imaging (DWI) (Figure 1B) images. Enhanced scans (Figure 1C) revealed uneven enhancement of the endometrium, clearly demarcated from the muscle layer. Multiple small cysts were observed in the upper segment of the cervix, arranged in clusters.

Case 2: Ultrasonography revealed that the endometrium was approximately 1.2 cm thick, with a distinct 1.8 cm polypoid nodule detected in the cervical canal. MRI examination indicated an endometrial thickness of 0.8 cm without obvious abnormalities. Nodules were identified within the isthmus of the uterus (Figure 2), extending into the cervical canal, with a diameter of 1.8 cm, which were considered to be endometrial polyps. The signal and enhancement characteristics of the endometrial polyps were similar to those of the endometrium.

Case 3: Ultrasonography indicated that the endometrium was approximately 0.4 cm thick. MRI findings revealed hydrops of the uterus. The endometrium was thin (Figure 3). Uterine effusion showed a high signal on T2WI (Figure 3A), higher signal on DWI (Figure 3B), but no enhancement (Figure 3C). Additionally, uneven signals were observed in the myometrium and upper region of the cervix, which were attributed to compression of the hydrops in the uterus.

FINAL DIAGNOSIS

Case 1

Renal-type adenocarcinoma in the endometrium, with cancerous tissue infiltrating less than 1/2 of the myometrium and down into the intercervical stroma (less than 1/2 wall thickness). The median renal-type adenocarcinoma involved both sides of the ovarian surface.

Case 2

Uterine sub-endometrial polyps, adenocarcinoma alterations, high-moderate differentiation, and infiltration of the myometrium at a depth less than half of the myometrial thickness. Additionally, the cancer foci were situated within the superficial layer of the cervix.

Case 3

Endometrial cancer Type II, serous carcinoma, focal clear cell carcinoma, invasive to the myometrium greater than 1/2 wall thickness, with visible vascular tumor thrombus, involving the cervical stroma (about 1/2 wall thickness).

TREATMENT

Case 1

The patient was treated by total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and para-aortic lymph node dissection. Postoperative radiotherapy and chemotherapy were performed.

Case 2

The patient was treated by total hysterectomy, followed by postoperative radiotherapy.

Case 3

The patient was treated by total hysterectomy, followed by postoperative radiochemotherapy.

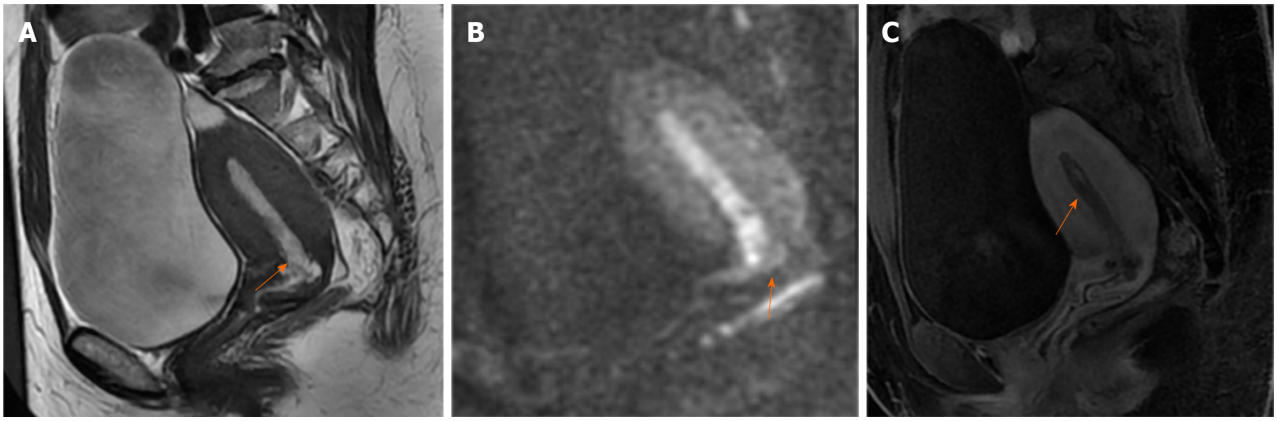

Figure 1 Endometrial carcinoma involving the cervical stroma in Case 1. A: On the T2WI image, the endometrium appears slightly thickened and extends downwards into the intra-cervical inlet area (arrow), showing a clear boundary with the cervix. The mucosa within this region exhibits a cyst; B: On the diffusion weighted imaging image, no obvious hyperintensity is evident in the endometrium, while the endocervical stroma appears hypointense (arrow); C: On the enhanced image, the endometrium does not exhibit uniform enhancement, with a distinct demarcation from the muscle layer (arrow).

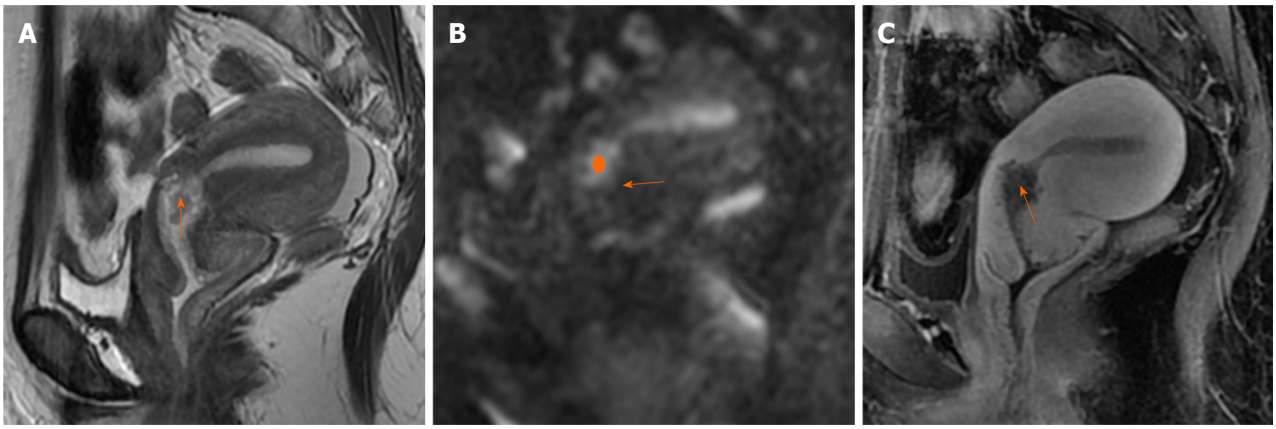

Figure 2 Endometrial carcinoma involving the cervical stroma in Case 2. A: On the T2WI image, polypoid nodules were observed within the mucosa of the intrauterine cervical orifice region (arrow), showing a clear boundary with the cervix; B: On the DWI image, the nodule exhibited a slightly hyperintense signal (circle), while the endocervical stroma displayed a hypointense signal (arrow); C: On the enhanced image, the nodule was marginally enhanced and distinctly separate from the endocervical stroma (arrow).

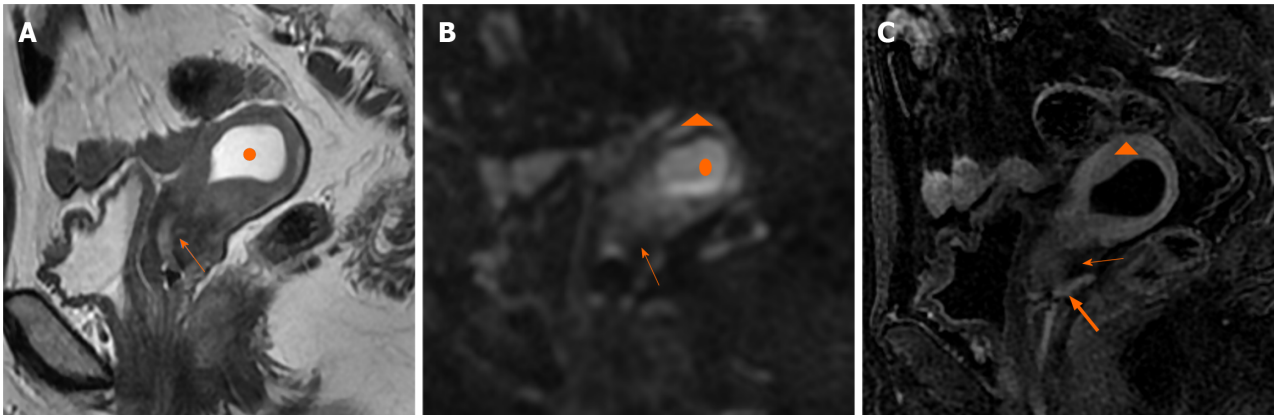

Figure 3 Endometrial carcinoma involving the cervical stroma in Case 3. A: On the T2-weighted imaging image, the endometrium cannot be seen, with fluid accumulation in the cavity (circle). The cervix stroma is depicted as low signal (arrow); B: On the diffusion weighted imaging (DWI) image, the fluid accumulation within the cavity is blood, and the DWI displays a slightly elevated signal (circle). Additionally, the myometrium exhibits a marginally high signal (triangle), while the cervix interstitial region maintains a low signal (arrow); C: On the enhanced image, the endometrium cannot be seen, while the muscle layer shows marked prominent enhancement (triangle). The cervical stroma shows hypo-enhancement (narrow arrow), but the mucosa is significantly enhanced (bold arrow).

OUTCOME AND FOLLOW-UP

Case 1

Surgery was performed approximately one and a half years prior to the present study. Postoperative bleeding following intercourse occurred. Pathological examination of the vaginal endoscopic biopsy suggested chronic inflammation of the mucosal tissue.

Case 2

At three years and two months post-surgery, there was no evidence of recurrence.

Case 3

No recurrence was observed after a period of 2 years and 9 months.

DISCUSSION

Endometrial carcinoma with cervical stromal invasion is associated with lymph node metastasis and poor survival[5]. Lymph node status is a key prognostic indicator of endometrial cancer, and sentinel lymph node localization can even detect micrometastases and change the patient's treatment regimen[6]. Therefore, correct diagnosis of cervical interstitial involvement is crucial. Currently, MRI is the best imaging tool for evaluation of endometrial cancer.

At present, the standard for cervical stromal invasion by MRI is as follows[7]: On T2WI, a medium-intensity tumor disrupts the low signal intensity of the cervical stroma; on contrast-enhanced imaging, a low-intensity tumor disrupts the normal enhancement of the cervical stroma; and on DWI, a high-intensity tumor disrupts the low-intensity cervical stroma. There are primarily two patterns of endometrial carcinoma invading the cervix[8,9]: The first involves the tumor infiltrating the uterine body and both the cervix mucosa and cervical stroma, while the second involves the tumor directly penetrating the cervical stroma through the myometrium, bypassing the cervix mucosa. Cases of endometrial carcinoma involving the cervical stroma without a distinct lesion in the endometrial cavity are rare, and their pathogenesis remain unclear.

In our cases, hysteroscopy and segmental curettage suggested atypical hyperplasia and polyps in the endometrium. MRI examination in Case 1 revealed a heterogeneous endometrium, with thickened endometrium extending downward to the endocervix. No malignant tumors were detected within the endometrium. Multiple cysts were observed on the surface of the cervix mucosa, but the stroma remained intact; thus, endometrial hyperplasia was diagnosed. MRI examinations of Case 2 revealed a nodule in the endocervix, with no evidence of invasion into the cervical stroma. Case 3 presented with hydrosalpinx and a non-thickened endometrium. The myometrium exhibited inconsistent enhancement, which was interpreted as a consequence of compression of the muscle layer. No lesions were found in the cervix. All three patients had either missed or misdiagnosed MRI results.

Similar to the findings in the present study, Taylor *et al*[10] reported four patients with endometrial hyperplasia exhibiting cervical stromal invasion. On pathological examination, it was found that the endometrium did not meet the criteria for endometrioid adenocarcinoma. This was consistent with dysplasia or no atypia, but cancerous foci had invaded the stromal layer of the cervix. They previously identified this undescribed phenomenon as likely due to the spread of endometrial hyperplasia into the cervix, secondary carcinogenesis, and invasion of the stromal layer of the cervix. They proposed designating it as stage II endometrial carcinoma. However, our cases differ from theirs in that our three patients had different types of endometrial carcinoma with varying grades, not limited to low-grade endometrioid adenocarcinoma.

Further assessment of Case 1 and Case 2, showed that their disease may be similar to the first type of invasion[8,9], where endometrial lesions (either polyps or hyperplasia) extending to the cervix, subsequently lead to secondary malignancy. These lesions then infiltrate into both the cervix mucosa and stroma, which is similar to the implantation invasion reported by Tambouret *et al*[11]. Case 3, may be identical to the second type of invasion, where cancer cells infiltrate the myometrium and then directly infiltrate the cervical stroma without accumulating in the cervical mucosa[8,9].

CONCLUSION

We describe a rare occurrence of endometrial carcinoma with cervical stromal invasion which presents a diagnostic challenge. When the criteria for endometrial carcinoma are not met, cervical stromal invasion may be present. We hope that our cases will enrich the diagnostic experience of radiologists, and help future research to discover the mechanism of this type disease. Furthermore, we advocate that clinicians should incorporate immunohistochemical results into routine hysteroscopy pathology assessments for a more comprehensive evaluation. This approach aims to prevent potential misdiagnoses and ensure appropriate treatment.

FOOTNOTES

Author contributions: Liu MM contributed to manuscript writing and editing, and data collection; Liang YT and Jin EH contributed to conceptualization and supervision; all authors have read and approved the final manuscript. Both Jin EH and Liang YT have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Jin EH conceptualized, designed, and supervised the whole process of the project. He searched the literature, revised and submitted the early version of the manuscript. Liang YT was instrumental and responsible for data re-analysis and re-interpretation, comprehensive literature search, preparation and submission of the current version of the manuscript. This collaboration between Jin EH and Liang YT is crucial for the publication of this manuscript and other manuscripts still in preparation. Jin EH takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication processes.

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CASE REPORT

IgG4-related sclerosing cholangitis associated with essential thrombocythemia: A case report

Zhi-Nian Wu, Ru JI, Ying Xiao, Ya-Dong Wang, Cai-Yan Zhao

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Abstract

BACKGROUND

The complexity of immunoglobulin G4 (IgG4)-related diseases and their potential connection to hematologic malignancies remains unclear. This article provided a review of the diagnosis and treatment of a patient with IgG4-related sclerosing cholangitis (SC) and essential thrombocythemia (ET), along with an analysis of relevant literature to enhance comprehension of this disease.

CASE SUMMARY

A 56-year-old male was admitted to two hospitals with deteriorating jaundice and pruritus prior to hospitalization. Beyond our expectations, the patient was first diagnosed with IgG4-SC and ET with the Janus kinase 2 V617F mutation. Interestingly, the administration of acetate prednisone significantly resulted in improvements in both IgG4-SC and ET. Clinicians need to pay attention to immune disorders and inflammation as they contribute to the development of various disease phenotypes.

CONCLUSION

When IgG4-SC is suspected without histopathological evidence, diagnostic therapy and long-term regular follow-up can lead to positive treatment outcomes. Clinicians should be mindful of the potential presence of concurrent hematologic diseases in patients with immune disorders.

Key Words: Immunoglobulin G4-related sclerosing cholangitis; Essential thrombocythemia; Autoimmune pancreatitis; Janus kinase 2 mutation; Glucocorticoids; Case report

Core Tip: The case diagnosed with immunoglobulin G4 (IgG4)-related sclerosing cholangitis (SC) and essential thrombocythemia was first reported. In this article, we described the clinical features of this case and reported the diagnosis and treatment process and prognosis. The relationship between IgG4-SC and Janus kinase 2 V617F mutation diseases was analyzed and summarized by retrieving literature.

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INTRODUCTION

Prior research identified a connection between autoimmune disorders and the development of myeloproliferative neoplasms (MPNs)[1]. Immunoglobulin G4 (IgG4)-related sclerosing cholangitis (SC) was first reported in Japan, and it refers to SC of unknown cause. It is characterized by increased serum IgG4 levels and fibrosis associated with marked infiltration of local lesions by lymphocytes and IgG4-positive plasma cells[2]. Precise epidemiological data are currently lacking, and the available data were mainly obtained in Japanese studies. The overall incidence and annual prevalence of IgG4-SC in Japan are 2.1 and 0.63 per 100000 people, respectively[2]. It is challenging to distinguish IgG4-SC from primary sclerosing cholangitis (PSC) and biliary cancer in the absence of histopathologic evidence[2].

Meanwhile, essential thrombocythemia (ET) is an MPN with an annual incidence of approximately 1.2-3.0 per 100000 people[3]. It is rare for patients to experience both ET and IgG4-SC simultaneously. We experienced a patient exhibiting jaundice, pruritus, a high platelet (PLT) count, and bleeding as clinical features. This was the first reported case both domestically and internationally of concurrent IgG4-SC and ET based on a review of the literature.

CASE PRESENTATION

Chief complaints

A 56-year-old male was admitted to our hospital on September 29, 2022 with progressive jaundice and intractable pruritus persisting for 1 mo.

History of present illness

The patient experienced poor appetite, abdominal distension, and intractable pruritus but did not report abdominal pain, diarrhea, rash, hemorrhagic spots, or ecchymosis prior to hospitalization. Prior to coming to our hospital, the patient had visited Municipal hospitals on September 15, 2022 and a tertiary hospital on September 23, 2022. The results of blood tests, as shown in Table 1, revealed significantly elevated serum biomarkers including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), and bilirubin. Additionally, the PLT counts in the peripheral blood were significantly higher than normal. A computed tomography scan revealed wall thickening in the cholecystic and common bile duct, along with narrowing in the common bile duct and pancreatic segment, with enlargement of the head of the pancreas, manifestation of pancreatic inflammation. Based on blood tests and imaging, clinicians diagnosed the presence of biliary space-occupying lesions. However, despite treatment, the patient's symptoms, such as jaundice and skin pruritus, did not improve.

History of past illness

The patient had no history of liver disease or hemopathy. There was also no record of taking drugs that could potentially cause liver injury in the prior 6 mo.

Personal and family history

The patient had no history of alcohol consumption, smoking, or genetic disease in the family.

Physical examination

The patient's temperature was 36.4 °C, heart rate was 72 beats/minute, and blood pressure was 134/71 mmHg. Severe jaundice was observed in the skin, mucous membrane, and sclera along with widespread scratches due to pruritus. No other regions showed any signs.

Laboratory examinations

On September 30, 2022, blood examinations were performed. The results were as follows: Total bilirubin 156.36 μmo1/L; direct bilirubin 126.66 μmo1/L; ALP 722 U/L; GGT 407 U/L; total bile acid 617 μmo1/L; and PLT counts 771 × 10^9/L. These levels were significantly elevated. Blood AST and ALT levels were mildly increased. The levels of serum pancreatic

Table 1 Main outcomes of laboratory tests at hospitalization

Variable	September 15, 2022	September 23, 2022	September 30, 2022	October 04, 2022	October 09, 2022	October 10, 2022	October 14, 2022	October 18, 2022	October 28, 2022
TBIL in μmol/L	151.79	186.78	156.36	135.41	123.79	99.15	83.87	134.00	53.00
ALP in U/L	895.2	856.2	722.0	837.0	1077.0	856.0	715.0	827.0	745.0
GGT in U/L	NA	393.3	407.0	475.0	709.0	580.0	469.0	889.0	1021.0
PLT as $\times 10^9$ /L	998	760	771	813	910	NA	804	1035	813
D-dimer in g/L	NA	NA	0.39	0.39	0.55	NA	1.45	2.33	NA
PT in s	11.4	NA	11.0	11.1	11.0	NA	10.9	9.9	NA
APTT in s	27.9	NA	42.5	35.6	42.5	NA	31.6	30.6	NA
INR	1.00	NA	0.99	1.00	0.99	NA	0.98	0.89	NA
FIB in g/L	3.68	NA	3.99	3.57	3.99	NA	3.72	3.48	NA
COL/EPI-CT in s	NA	NA	NA	NA	NA	NA	> 292	NA	NA
COL/ADP-CT in s	NA	NA	NA	NA	NA	NA	244	NA	NA
P2Y12-CT in s	NA	NA	NA	NA	NA	NA	136	NA	NA

ALP: Alkaline phosphatase; APTT: Activated partial thromboplastin time; COL/ADP-CT (s): Collagen–adenosine diphosphate closure time(s) (normal range: 62-100s); COL/EPI-CT (s): Collagen–epinephrine closure time (s) (normal range: No drugs, 82-150 s; drugs, 193-300 s); FIB: Fibrinogen; GGT: γ-glutamyl transpeptidase; INR: International normalized ratio; NA: Not available; P2Y12-CT(s): Purinergic receptor P2Y, G protein-coupled 12- closure time (s) (normal range: 106-300s); PLT: Platelet; PT: Prothrombin time; TBIL: Total bilirubin. COL/EPI-CT, COL/ADP-CT, P2Y12-CT are indicators of platelet function, and larger values indicate lower platelet function.

enzymes were in the normal range. There was no infectious evidence of hepatitis A-E virus, HIV, Epstein-Barr virus, and cytomegalovirus. The levels of serum tumor markers, including ferritin 354.74 ng/mL (normal range: 23.9-33.6 ng/mL), carbohydrate antigen 199 367.4 U/mL (normal range: 0-25 U/mL), protein induced by vitamin K absence or antagonist-II 80.54 mAU/mL (normal range: 0-40 mAU/mL), and carbohydrate antigen 125 36.5 U/mL (normal range: 0-35 U/mL) were elevated, while alpha-fetoprotein and carcinoembryonic antigen levels were normal. The outcomes of the extractable nuclear antigen polypeptide antibody spectrum, anti-neutrophil cytoplasmic antibodies, and liver-related antibodies such as anti-liver-kidney microsomal, anti-smooth muscle, anti-soluble liver antigen, and anti-mitochondrial antibodies were negative. The serum IgG 20.4 g/L (normal range: 7.51-15.6 g/L) levels were also high.

Imaging examinations

Magnetic resonance imaging revealed dilation of the intrahepatic bile duct, local narrowing, and uneven thickness of the bilateral hepatic duct, common hepatic duct, and lower segment of the common bile duct. The head of the pancreas was enlarged, and the imaging physician considered possible localized pancreatitis (Figure 1).

Further diagnostic work-up

Unfortunately, jaundice did not vanish gradually. At the same time, PLT levels progressively increased (813 × 10^9/L) starting on October 4, 2022. To prevent thrombosis development and embolism because of significantly high PLT counts, aspirin (0.1 g per day) and low-molecular-weight heparin (4250 IU q12h ih) were administered. After 4-d anticoagulation and anti-PLT therapy, ecchymosis and a lump with tenderness were found at the needle sites and the back of the left lower leg, respectively. Color doppler ultrasound showed a liquid mass in the muscle layer of the left lower leg, and there were no signs of clot or deep vein thrombosis in the legs. We considered the lump a hematoma. Therefore, aspirin and low-molecular-weight heparin were discontinued immediately.

According to the above clues, the cause of jaundice in patients may be any of the following: PSC; IgG4-SC; and tumor. Due to the patient's high risk of bleeding, a liver biopsy was not conducted. This decision complicated the process of distinguishing between PSC and a bile duct tumor, but quantitative analysis of immunoglobulin subclasses was carried out. The coagulation function examination suggested a normal or hypercoagulable state and decreased PLT function (Table 1). To determine the cause of hyperthrombocytosis and bleeding, we conducted bone marrow and genetic testing.

The outcomes of the examinations were gradually reported. Quantitative analysis of immunoglobulin subclasses: Serum IgG4 (19 g/L, normal range: 0.03-2.01 g/L) level was significantly elevated. Bone marrow cytology examination and bone marrow histopathology are depicted in Figure 2. Gene testing found that the Janus kinase 2 (*JAK2*) V617F mutation was positive.

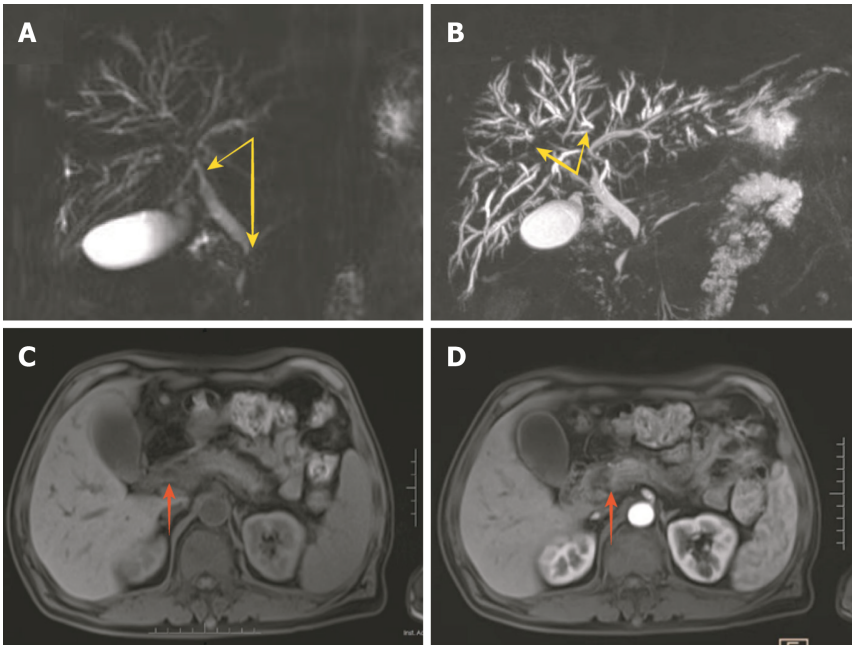

Figure 1 Magnetic resonance imaging of the bile ducts. A and B: Magnetic resonance cholangiopancreatography revealed dilation of the intrahepatic bile duct and local narrowing in the bilateral hepatic duct, common hepatic duct, and lower segment of the common bile duct (yellow arrows); C and D: Plain and enhanced magnetic resonance imaging showed an enlarged pancreatic head. Possible local inflammation was, but there was no delayed enhancement (red arrows).

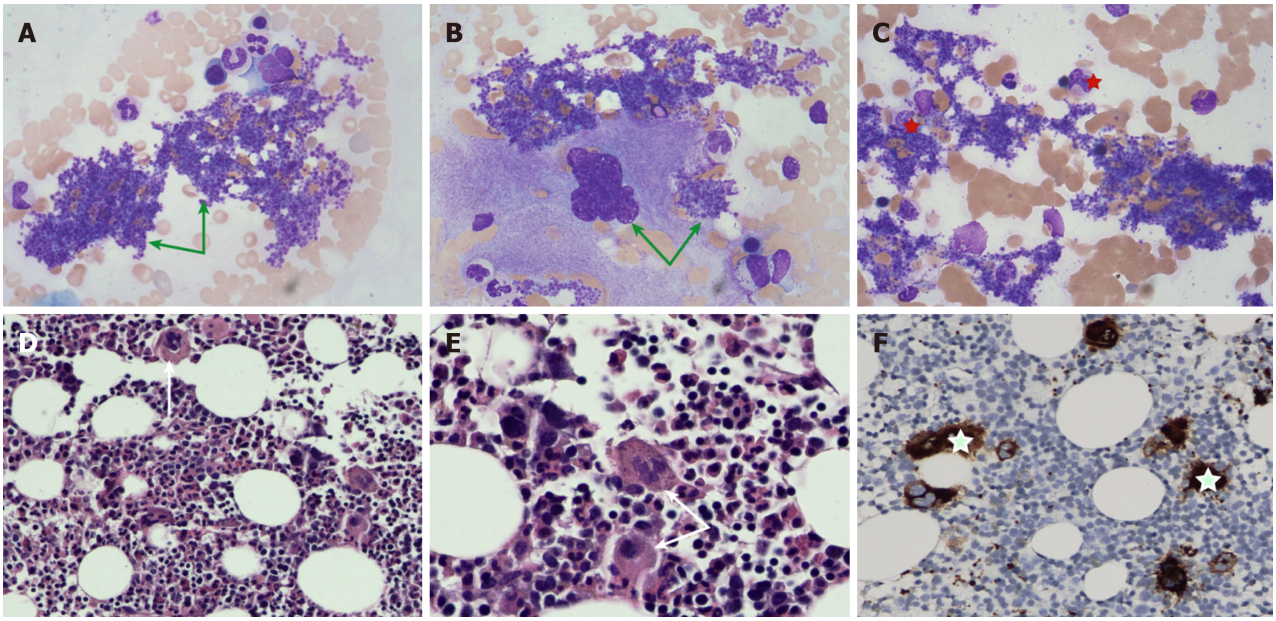

Figure 2 Bone marrow examination. A and B: Platelets existed in the form of piles and pieces in the peripheral blood smear and bone marrow smear (green arrows); C: Proplatelet-producing megakaryocytes were markedly increased in the bone marrow smear (red five-pointed star); D and E: The number of megakaryocytes was significantly elevated, especially megakaryocytes with large cell bodies and hyperlobated nuclei, and they were isolated or arranged in dense clusters (reticular fibrosis grade of MF-1) (Hematoxylin-eosin staining: 200 times, 400 times) (white arrows); F: CD61 immunohistochemistry was also positive on megakaryocytes (green five-pointed star).

FINAL DIAGNOSIS

Although pancreatic enzymes did not show significant abnormalities, localized pancreatitis was still be considered in conjunction with imaging studies conducted before and after hospital admission. Based on the significantly elevated IgG4 levels, we concluded that the patient's diagnosis was autoimmune pancreatitis. Additionally, the clinical presentation of this patient was mainly jaundice, and imaging findings showed significant bile duct abnormalities, therefore the final diagnosis included IgG4-SC[4]. ET was diagnosed in the patient in accordance with relevant guidelines (Table 2)[5].

Table 2 Criteria for diagnosis of essential thrombocythemia

Major criteria	Minor criteria
Platelet count ≥ 450000 per mm^3	Presence of clonal marker or of evidence of reactive thrombocytosis
Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobated nuclei; no substantial increase or left shift in neutrophil granulopoiesis or erythropoiesis; in rare instances, minor (grade 1) increase in reticulin fibers	
Criteria for BCR-ABL1-positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, or other myeloid neoplasm not met; *JAK2* V617F, *CALR*, or *MPL* mutation.	

Diagnosis requires all major criteria or the first three major criteria plus a minor criterion. *CALR*: Calreticulin; *JAK2*: Janus kinase 2; *MPL*: Myeloproliferative leukemia.

TREATMENT

At admission, the patient was given symptomatic treatments, including liver protection and choleretic treatment. The patient (body weight: 65 kg) was treated with oral glucocorticoids (acetate prednisone tablets, 30 mg, once daily) combined with hydroxyurea tablets (500 mg, twice daily).

OUTCOME AND FOLLOW-UP

The patient's jaundice resolved, and he was discharged on October 20, 2022. One month after discharge, the patient stopped taking hydroxyurea tablets by himself. The dosage of corticosteroids was gradually reduced. Follow-up was conducted 7 mo later by phone. Jaundice and hematoma had subsided, and the bleeding tendency had disappeared. Bilirubin levels and PLT counts gradually return to normal (Figure 3).

DISCUSSION

IgG4-SC is an autoimmune disease closely associated with IgG4 and falls under the umbrella of IgG4-related diseases. These conditions are known for causing ongoing chronic inflammation in individuals who have not received treatment. Glucocorticoids are recommended as the first-line treatment therapy for IgG4-SC[4].

ET is a kind of MPN characterized by the proliferation of bone marrow megakaryocytes and increased PLT counts in peripheral blood[5]. The diagnosis of ET is mainly based on the diagnostic criteria proposed by Tefferi and Pardanani[5] in 2019, and this case fulfills all the diagnostic criteria. Low-dose aspirin (81-100 mg, once daily), hydroxyurea (500 mg, twice daily), or interferon alpha-2α (45 μg once a week, the maximum dose of 180 μg once a week) should be given for patients diagnosed with ET until normal PLT counts[5,6]. It is well-known that glucocorticoids promote PLT production, which will not be conducive to the treatment of ET. Therefore, whether glucocorticoids should be used in this patient became a topic to be discussed by clinicians.

To enhance our understanding of the pathogenesis of ET, we conducted an extensive literature review. Chronic inflammation is considered a prerequisite for defending against clonal evolution and cancer development due to its effective DNA repair mechanism in response to sustained oxidative stress caused by chronic inflammation[7]. It is important to note that mutations resulting from DNA repair mechanisms may also increase the risk of clonal evolution. Early studies have shown that sustained inflammation can activate JAK2 (including the V617F mutation) and lead to genome instability, increasing the risk of mutation[8]. Further, chronic inflammation has been demonstrated to be an important driver of ET[7,9]. Therefore, it was not unexpected that this patient suffered from IgG4-SC and ET.

IgG4-SC is an autoimmune disease closely related to IgG4 and is classified as one of the IgG4-related diseases. These diseases are known for causing persistent chronic inflammation in untreated individuals. Emerging evidence indicates that the pathophysiological mechanisms linked to immune inflammation could potentially affect PLT production. Kristinsson *et al*[1] confirmed that autoimmune diseases (such as immune thrombocytopenic purpura, Crohn's disease, polymyalgia rheumatica, giant cell arteritis, Reiter's syndrome, and aplastic anemia) increase the risk of MPN by 20%, especially ET[1]. PLT counts have significant variability in immune-mediated conditions, specifically, ET and immune thrombocytopenic purpura can interconvert in different immune states[10].

During follow-up of this case, the patient came to our clinic again due to weakness, and examination showed ALT 637 U/L, AST 394 U/L, total bilirubin 38.8 μmo1/L, direct bilirubin 27.6 μmo1/L, GGT 1141 U/L, ALP 1285 U/L, WBC 14.46 × 10^9/L, N% 75.4%, eosinophil 0.88 × 10^9/L, and PLT 1461 × 10^9/L (because of poverty, the patient did not receive inpatient treatment). Multiple simultaneous increases in biliary enzymes and PLT counts further supported a potential link between IgG4-SC and ET.

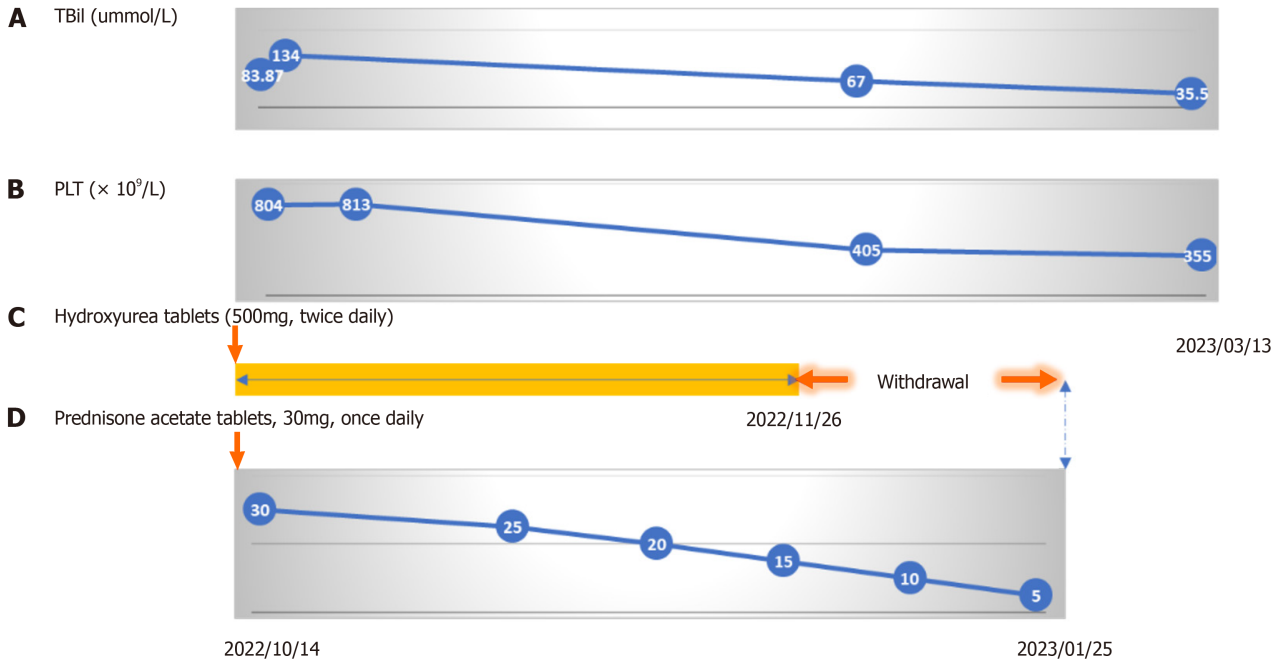

Figure 3 Follow-up procedure. A and B: Changes in total bilirubin (TBIL) and platelets (PLT) in the patient during the treatment process; C: Hydroxyurea (500 mg 2/d) was self-discontinued after 1 mo; D: Acetate prednisone tablets were reduced by 5 mg after the first 2 wk, followed by a weekly reduction of 5 mg. The patient self-discontinued the medication after 3 mo of use.

Mechanistically, aberrant B cell activation is present in both diseases[11,12]. This suggests that the presence of IgG4-SC and ET in this case is not merely a combination of the two diseases but rather distinct manifestations triggered by inflammatory and immune-related factors. Based on these theories, JAK inhibitors hold promise as alternative treatment options for IgG4-related diseases and MPNs[13,14]. Importantly, this case study can aid clinicians in expanding their diagnostic and treatment approaches.

CONCLUSION

IgG4-SC can be challenging to diagnose as it lacks specific clinical manifestations and can be mistaken for biliary malignancies, particularly when obtaining pathological examination results is difficult. Long-term follow-up and glucocorticoid treatment play a crucial role in establishing a definitive diagnosis. Furthermore, this manuscript explored the potential mechanistic connection between IgG4-SC and ET, expanding clinicians' perspectives on diagnosis and treatment strategies.

FOOTNOTES

Author contributions: Wu ZN and Xiao Y accessed the literature and wrote the case; Ji R and Zhao CY provided material support for the study; Wang YD served as the corresponding author and critically reviewed and revised the manuscript; All authors wrote the manuscript and approved this version to be submitted.

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CASE REPORT

Are all primary omental infarcts truly idiopathic? Five case reports

Haldun Kar, Danial Khabbazazar, Nihan Acar, Şebnem Karasu, Halis Bağ, Fevzi Cengiz, Osman Nuri Dilek

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Abstract

BACKGROUND

Idiopathic omental infarction (IOI) is challenging to diagnose due to its low incidence and vague symptoms. Its differential diagnosis also poses difficulties because it can mimic many intra-abdominal organ pathologies. Although hypercoagulability and thrombosis are among the causes of omental infarction, venous thromboembolism scanning is rarely performed as an etiological investigation.

CASE SUMMARY

The medical records of the 5 cases, who had the diagnosis of IOI by computed tomography, were examined. The majority of the patients were male (n = 4, 80%) and the mean age was 31 years (range: 21-38). The patients had no previous abdominal surgery or a history of any chronic disease. The main complaint of all patients was persistent abdominal pain. Omental infarction was detected in all patients with contrast-enhanced computed tomography. Conservative treatment was initially preferred in all patients, but it failed in 1 patient (20%). After discharge, all patients were referred to the hematology department for thrombophilia screening. Only 1 patient applied for thrombophilia screening and was homozygous for methylenetetrahydrofolate reductase (A1298C mutation) and heterozygous for a factor V Leiden mutation.

CONCLUSION

IOI should be considered in the differential diagnosis in patients presenting with progressive and/or persistent right side abdominal pain. Investigating risk factors such as hypercoagulability in patients with IOI is also important in preventing future conditions related to venous thromboembolism.

Key Words: Omental infarction; Acute abdominal pain; Thrombophilia screening; Factor V Leiden; Methylenetetrahydrofolate reductase; Case report

Core Tip: Idiopathic omental infarction is a rare cause of acute abdominal pain and should be considered in the differential diagnosis in patients presenting with progressive right side abdominal pain. Omental infarction is idiopathic in cases whose etiology could not be established. Although hypercoagulability and thrombosis are among the causes of omental infarction, venous thromboembolism screening is rarely performed as an etiological investigation. Investigating risk factors such as hypercoagulability in patients with idiopathic omental infarction is crucial in preventing future conditions related to venous thromboembolism.

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INTRODUCTION

Idiopathic omental infarction (IOI), which is a rare cause of acute abdominal pain, was first described by Bush in 1896. It is an acute vascular pathology that develops as a result of impaired perfusion of the greater omentum[1,2]. Due to its low incidence and vague symptoms, it is challenging to diagnose without the support of radiological evidence. In most cases, IOI is confused with acute appendicitis or acute cholecystitis since the pain is mainly localized in the right side of the abdomen[3,4]. Omental infarction (OI) was named as primary and/or idiopathic in cases whose etiology could not be established. Although hypercoagulability and thrombosis are among the causes of OI, venous thromboembolism (VTE) screening is rarely performed as an etiological investigation[2]. In this study, we aimed to present 5 cases of IOI in the light of the current literature and to evaluate the place for VTE screening in etiology.

CASE PRESENTATION

Chief complaints

The main complaint of all patients was persistent abdominal pain, and the mean duration of pain prior to hospital admission was 3.5 d.

History of present illness

None of the patients had a history of regular drug use. The majority of the patients were male (n = 4, 80%) and the mean age was 31.4 years (range: 21-38). The demographics and the clinical features of the patients are summarized in Table 1.

History of past illness

The patients had no previous abdominal surgery or a history of any chronic disease.

Personal and family history

No family history of liver disease, bleeding disorder, or other coagulopathy was detected in any patient.

Physical examination

One of the patients had an acute abdomen examination. Other patients had abdominal tenderness.

Laboratory examinations

Laboratory tests were unremarkable.

Imaging examinations

Computed tomography (CT) scan was performed in all cases (Figures 1 and 2). Omental fat thickening and stranding were detected as common findings without any accompanying abnormality on CT scans.

Table 1 Demographics, clinical data, and laboratory and computed tomography findings of the patients

Patient number	1	2	3	4	5
Age in yr	21	28	34	36	38
Sex	M	F	M	M	M
Smoking status	Yes	No	Yes	Yes	Yes
Duration of symptoms in d	2	3	2	7	5
Pain localization	Epigastrium	URQ	Epigastrium/LRQ	URQ	URQ
Peritoneal irritation sign	No	No	Yes	No	No
CT localization	URQ, inframesocolic omentum	URQ, anterior to the ascending colon	ULQ, inframesocolic omentum	URQ, lateral to the hepatic flexura	URQ, inframesocolic omentum
Lesion diameter in mm	40 × 85	35 × 45	23 × 32	40 × 73	52 × 58
BMI in kg/m^2	24	26	24	23	24
WBC as $10^9/L$	10.94	16.87	15.29	8.64	6.77
CRP 0-5 mg/L	2.13	0.02	2.99	5.88	8.70
PT 9.4-12.5/s	13.1	10.1	14.2	12.5	11.3
CK 30-200 U/L	261	93	142	297	287
Management	Medical	Medical	Surgical	Medical	Medical
LOS in d	5	4	3	2	5

BMI: Body mass index; CK: Creatine kinase; CRP: C-reactive protein; CT: Computed tomography; F: Female; LOS: Length of stay; LRQ: Lower right quadrant; M: Male; PT: Prothrombin time; ULQ: Upper left quadrant; URQ: Upper right quadrant; WBC: White blood cell count.

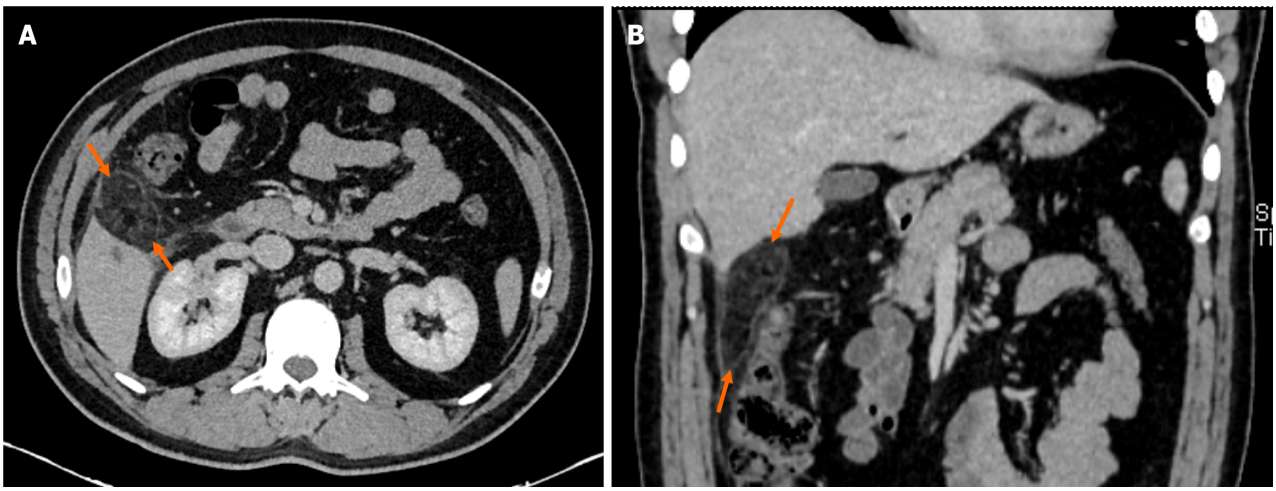

Figure 1 Omental infarction in a 36-year-old male. A and B: On contrast enhanced transverse (A) and coronal reformat (B) computed tomography images, fat thickening and stranding in omentum in the right upper quadrant formed an approximately 8 cm mass-like lesion with hyperdense peripheral halo (arrows).

FINAL DIAGNOSIS

Physical examination, laboratory tests, and abdominal ultrasound as the primary diagnostic approaches were insufficient for the definitive diagnosis. OI was diagnosed in all patients with contrast-enhanced CT by an experienced gastrointestinal radiologist. Thus, patients were able to receive the appropriate management after the definite diagnosis.

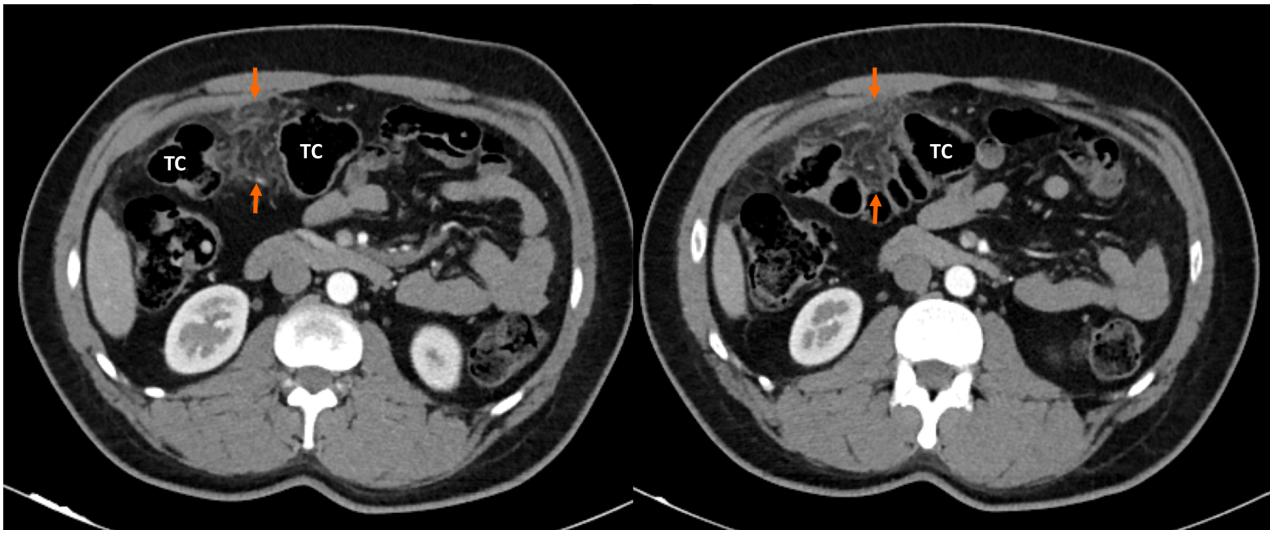

Figure 2 Omental infarction in a 38-year-old male. On contrast enhanced transverse computed tomography images, focal area of fat thickening and stranding (arrows) was seen in the omentum adjacent to the transverse colon (TC).

TREATMENT

Medical treatment (oral intake restriction, analgesics, proton pump inhibitors, antiemetics, and antibiotics) was administered to all patients. The mean duration of hospitalization was 3.8 d. Only 1 patient, who developed diffuse peritonitis, required surgical intervention on the 2nd day of the conservative follow-up. During the operation, an OI zone with a diameter of 3 cm adjacent to the mid-transverse colon was found in accordance with CT (Figures 3 and 4). No other abdominal pathology was observed during the exploration. Partial omental resection and appendectomy were performed. Pathological examination of the specimen revealed omental edema, congestion, and venous dilatation/thrombosis.

OUTCOME AND FOLLOW-UP

The postoperative course was uneventful, and the patient was discharged without any complications. On the 8th day after discharge, the same patient presented with abdominal distension, constipation, nausea, and vomiting and was hospitalized with the diagnosis of adhesive ileus. Since the clinical process was unresponsive to the conservative management, the patient was re-operated. The other 4 patients who received medical treatment were discharged without any problems. After discharge, all patients were referred to the hematology department for thrombophilia screening. Thrombophilia screening was performed on 1 patient who applied to the hematology outpatient clinic. The patient was homozygous for methylenetetrahydrofolate reductase (MTHFR) (A1298C mutation) and heterozygous for a factor V Leiden mutation. Anticoagulant therapy was started.

DISCUSSION

Although IOI is rare, advances and increasing accessibility in radiologic techniques have increased the incidence of this condition. It has an incidence equivalent to less than 4 cases per 1000 appendicitis cases[5,6]. Eighty-five percent of OI cases were reported as adult patients, and the cases were between 30-50 years of age. It is twice as common in males than in females[7,8]. In our case series, the mean age was 31.4 years, and the rate of male patients was 80% in accordance with the literature.

Omental infarcts are divided into two main groups according to the pathogenesis as primary and secondary. Secondary infarcts develop due to the causes of venous thrombosis (*e.g.*, hypercoagulability, vasculitis, polycythemia, and vascular anomalies) and omental torsions caused by cysts, tumors, hernias and adhesions. The pathogenesis of IOI has not been clearly determined, but anatomical malformations such as bifurcated or accessory omentum, sudden movements, vigorous exercise, heavy food intake, hyperperistalsis, and obesity have been introduced as predisposing factors[4,9]. There are studies showing that obesity is an important risk factor, especially in the pediatric patient group[10,11]. None of the patients from our case series were obese.

OI has been reported to occur more frequently on the right side. Many authors have suggested that the omentum has an abnormal and fragile vasculature in the right quadrant and is consequently more susceptible to infarction[12,13]. As another reason, the omentum is longer and more mobile in the right side[7]. In our series, the OI was located in the right upper quadrant in 4 cases (80%).

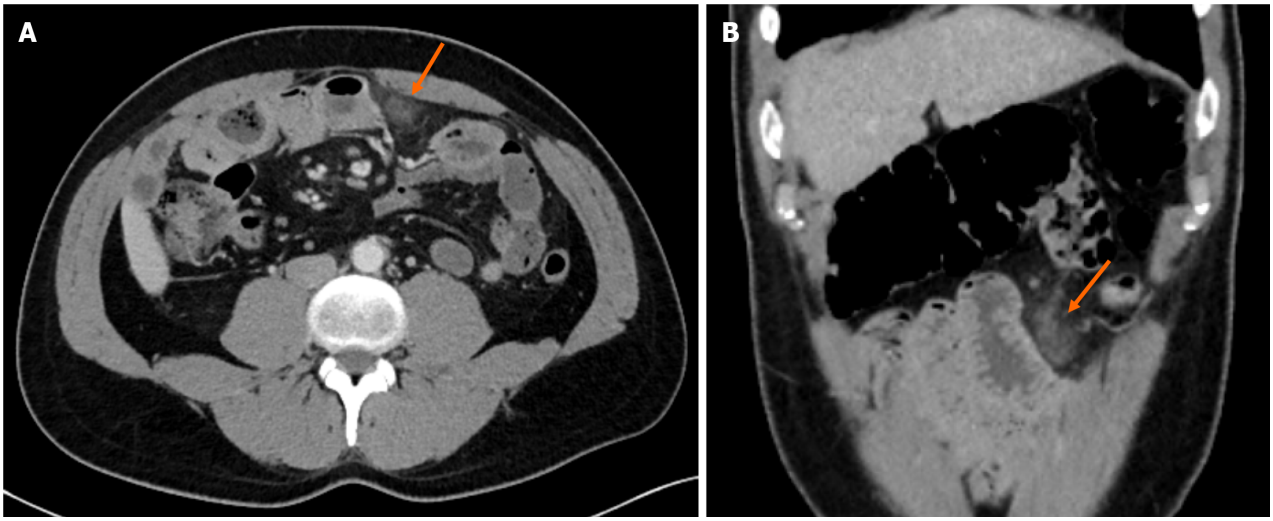

Figure 3 Omental infarction in a 34-year-old man. A and B: On contrast enhanced axial (A) and coronal (B) computed tomography images, a mass like focal hyperdensity with peripheral fat stranding was seen in the left inframesocolic omentum (arrows).

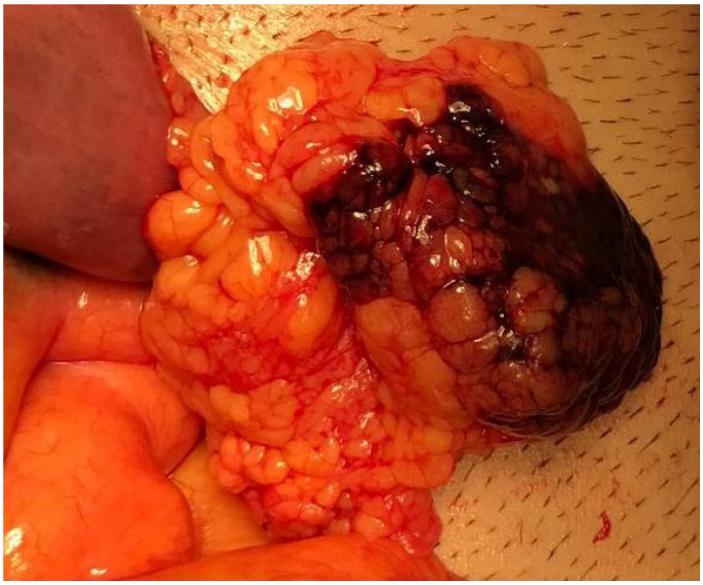

Figure 4 The appearance of the omental infarction.

One of our five patients, who was initially considered as IOI, was then diagnosed as secondary OI since the patient was homozygous for the MTHFR A1298C mutation and heterozygous for a factor V Leiden mutation after thrombophilia screening. MTHFR is a homocysteine metabolic regulatory enzyme. Mutations in the MTHFR gene reduce enzyme activity and thus increase plasma homocysteine. Hyperhomocysteinemia can destroy the vascular endothelium and alter blood coagulation status as well as platelet function and eventually participate in the pathogenesis of VTE[14].

Factor V Leiden mutation is the most common genetic risk factor for VTE. It is characterized by a weak anticoagulant response to activated protein C. Population studies have shown that approximately 10% of factor V Leiden heterozygotes develop VTE during their lifetime. This rate can be up to 25%-40% in thrombophilic families. It has also been reported that the risk of VTE is further increased in factor V Leiden heterozygotes accompanied by obesity and minor trauma[15,16].

This actually overlaps with the predisposing factors predicted for IOI. When the case reports and series of OI from the early 2000s to the present were reviewed, it was observed that thrombophilia screening was performed in 6 cases (Table 2). While 4 cases were found to be non-determined[3,17-19], the other case was diagnosed with antiphospholipid syndrome and presented as secondary OI[20]. In the last case, protein C and protein S deficiency was detected in the thrombophilia screening performed on the development of thrombosis in the superior mesenteric vein in the early period after OI[21].

In addition, D-dimer and fibrin degradation products were also investigated and were higher in some publications [10]. Although the fact that which patients should be screened for thrombophilia is still a controversy in the literature, it has been stated that screening can be beneficial in thrombosis of unusual areas such as spleen, mesentery, and liver[22].

Table 2 Previously reported omental infarct cases with thrombophilia work-up

Ref.	Age in yr/sex	Hypercoagulable states	Treatment
Lindley and Peyser[3]	42/male	Unremarkable	Surgical (laparoscopic)
Subasinghe *et al* [17]	37/male	Unremarkable	Surgical
Kaya *et al*[18]	25/male	Unremarkable	Medical
Porras *et al*[19]	11/male	Unremarkable	Medical
Alshehri *et al*[20]	46/male	Antiphospholipid syndrome	Medical
Patle *et al*[21]	41/female	Protein C and protein S deficiencies	Surgical (laparoscopic)
Present case	38/male	Homozygous for methylenetetrahydrofolate reductase (A1298C) mutation and heterozygous for factor V Leiden mutation	Medical

Considering the progressive edema and hemorrhagic necrosis secondary to the venous stasis and thrombosis in the pathophysiology of the disease, questioning the history of VTE carefully in these patients and their families, and consulting hematology in terms of thrombophilia screening may be beneficial[7].

Although OI usually occurs on the right side of the omentum, it can develop wherever the omental tissue is present [20]. Therefore, the chief complaint in 90% of the cases is right upper and/or lower quadrant abdominal pain[5,23]. Acute appendicitis, acute cholecystitis, acute pancreatitis, renal colic, acute diverticulitis, and epiploic appendicitis are primarily considered in differential diagnosis[2,24]. IOI has no early specific symptoms and is usually characterized by progressive, persistent abdominal pain. Physical examination may reveal the signs of peritoneal irritation from mild, localized irritation to generalized peritonitis. The mass can be palpated depending on the patient's body structure and the size of the omental tissue involved[4]. Consistent with the literature, abdominal pain was predominantly located in the right side of the abdomen in our cases.

In the past, the diagnosis of OI was often made incidentally during the laparotomies performed for acute abdomen, but today abdominal CT imaging has become the gold standard for diagnosis[1,4]. OI demonstrates different imaging findings on CT. It generally appears as a mild haziness or a large (> 5 cm) fatty, encapsulated mass, with stranding adjacent to the colonic segments, especially in the ascending colon. The adjacent colon is usually spared, but reactive colonic wall thickening can be seen[25]. On ultrasound, a hyperechoic, incompressible oval mass can be detected in the area of maximum tenderness[26].

Currently, there is no standard treatment modality for OI. Basically, there are two options: Conservative (medical) treatment and early laparoscopic surgical intervention[2]. Conservative treatment is recommended for the first 24-48 h if a confirmed diagnosis of OI can be made by typical clinical signs and imaging studies[6]. Intravenous fluid therapy, analgesics, antiemetics, and antibiotics are the first-line treatments combined with stopping or reducing oral intake. However, if the diagnosis is doubtful or conservative treatment fails, surgical exploration should be performed without delay[2,27].

The consensus of the supporters of conservative treatment is that OI is a self-limiting pathology, and this hypothesis is encouraged by long-term CT follow-ups. The risks of anesthesia and surgery that may arise as a result of surgical intervention are also eliminated[20]. On the other hand, those who recommend early surgical intervention advocate that both symptom control and patient discharge can be achieved earlier with surgery. They also suggest that removing the distorted omental tissue will theoretically reduce the likelihood of abscess and secondary adhesions[7].

In patients scheduled for surgical intervention, a laparoscopic approach is initially recommended for the lower morbidity[5,27]. In their systematic review, Medina-Gallardo *et al*[8] stated that conservative treatment was effective in most patients, but surgery had the advantage in terms of length of hospital stay. Young age and leukocytosis ≥ 12000/μL were found to be predictive factors for conservative treatment failure. The only patient in whom the conservative treatment failed in our series, had leukocytosis of 15000/μL and was 34-years-old, and this was consistent with the literature data. It should also be considered that the patients who underwent surgical intervention may be candidates for reoperations, as in our case. Therefore, patient selection for the surgical approach should be performed meticulously.

CONCLUSION

Although IOI is difficult to recognize with primary diagnostic methods, it can be easily diagnosed by CT and can be treated conservatively. Thus unnecessary surgery and anesthesia risks can be avoided. OI can occur anywhere omental tissue is present. Therefore, diseases such as acute appendicitis, acute cholecystitis, acute pancreatitis, renal colic, acute diverticulitis, and epiploic appendicitis should be kept in mind in the differential diagnosis. Investigating risk factors such as hypercoagulability in patients with IOI is also important in preventing future conditions related to VTE.

FOOTNOTES

Author contributions: Kar H, Khabbazazar D, and Acar N participated in the acquisition, analysis, and interpretation of the data and drafted the initial manuscript; Karasu Ş, Bag H, Cengiz F, and Dilek ON revised the article critically for important intellectual content.

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CASE REPORT

Seven-years post allogeneic hematopoietic stem cell transplantation pure red cell aplastic anemia cured with daratumumab: A case report and review of literature

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Abstract

BACKGROUND

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is currently the only viable method of curing patients with acute myeloid leukaemia. In 30% to 50% of patients, donors and recipients have some level of ABO blood group incompatibility. ABO blood group incompatibility can cause antibodies against the donor's red blood cells to persist in the recipient's body, resulting in a delay of several months in the recovery of red blood cells. A number of different treatments have been reported for post-transplant pure red cell aplastic anaemia (PRCA), such as plasmapheresis, donor lymphocyte infusions, anti-thymocyte globulin, rituximab and steroids.

CASE SUMMARY

A 41-year-old female diagnosed with acute myeloid leukaemia underwent peripheral blood allogeneic haematopoietic stem cell transplantation in November 2013 from an HLA matched unrelated donor. The donor was AB-positive and the recipient was O-positive. The patient was diagnosed with PRCA three months after receiving the donor stem cell transplant. After failing multiple lines of therapy, the patient applied for daratumumab. After receiving three doses of daratumumab, the patient developed a reticulocyte response and no longer required

blood transfusions.

CONCLUSION
The use of daratumumab anti-CD38 for the remove of plasma cells is safe and effective and may be tried for refractory patients with PRCA after undergoing allo-HSCT for ABO incompatibility.

Key Words: Transplantation; PRCA; Daratumumab; Leukemia; blood-group; Case report

Core Tip: Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is currently the only possible way to cure patients with malignant hematologic diseases. In Allo-HSCT, donors have some degree of ABO blood-group incompatibility with the recipient. An outcome of ABO incompatibility caused is pure red cell aplastic anemia (PRCA). We report a 41-year-old female diagnosed with acute myeloid leukemia received a peripheral blood allo-HSCT from an HLA-matched unrelated donor in November 2013. The patient was diagnosed with PRCA three months after allo-HSCT. After failing multiple lines of treatment, daratumumab was requested. After receiving three doses of daratumumab, the patient had a marked reticulocyte response and become transfusion independent.Using of anti-CD38 therapy with daratumumab to target residual host plasma cells is safe and effective, and it can be considered in refractory recipients with PRCA after allo-HSCT secondary to ABO incompatibility.

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INTRODUCTION

The incidence rate of pure red cell aplasia (PRCA) after transplantation is 6%–30%, and it varies with conditioning. Host hematopoietic function may persist after nonmyeloablative stem cell transplantation, and for a considerable duration, host and donor hematopoietic and immune functions may coexist (mixed chimerism). The risk of PRCA is increased when the blood type of the recipient is O and the blood type of the donor is A[1,2]. These patients often have undetectable reticulocytes, become dependent on red blood cell infusion, and are at risk of transfusion-related iron overload. Current treatments include tapering immunosuppressants, erythropoietin, glucocorticoids, plasmapheresis, rituximab, and donor lymphocyte infusion. CD38 is expressed at high levels in plasma cells and Daratumumab is a human IgG1κ monoclonal antibody against CD38. Considering that pure red cell aplastic anemia after transplantation is a pathophysiological change caused by antibodies produced by residual plasma cells of the recipient, we hypothesised that selective elimination of pathogenic plasma cell populations could overcome refractory erythrocyte-only aplastic anaemia. There have also been sporadic reports of successful use of daratumumab in patients with post-transplant pure red cell aplastic anemia[3-11] (Table 1). We present a patient who had pure red cell aplasia for 7 years, successfully treated with daratumumab after HLA-matched unrelated transplantation. This was the longest post-transplantation case reported in the literature but was still effectively treated after using daratumumab.

CASE PRESENTATION

Chief complaints

A 41-year-old female patient was admitted to our center 7 years ago due to gingival bleeding and was diagnosed with acute myeloid leukemia M2. Cytogenetic tests showed no positive findings.

History of present illness

After chemotherapy, the patient achieved complete remission and received unrelated HLA 10/10 matched hematopoietic stem cell transplantation (HSCT) (AB + donor, O + recipients). On + 106 days after transplantation she was diagnosed as PRCA, and she failed multiple therapies for it.

History of past illness

Conditioning began on November 17, 2013, performed with busulfan and cyclophosphamide + antithymocyte globulin (BU/CY + ATG) regimen. She received peripheral blood hematopoietic stem cells and CD34 + cells and mononuclear cell count was 4.67106/kg and 6.11108/kg, respectively. After transplantation, on day 11, neutrophil engraftment (0.65109/L)

Table 1 Summary of daratumumab utilization in post-transplant major ABO mismatched hematopoietic stem cell transplantation and delayed red blood cell engraftment

Ref.	Age/sex	Diagnosis	Type of transplant	ABO mismatch (D/R)	Conditioning	Source	GVHD prophylaxis	CD34+ cells (× 10^6/kg)	Neutrophil	Platelet	Previous therapies	Initiation	Doses	Time to response
Grigg *et al*[15]	17/F	SAA	MSD	B/O	FLU + Cy + ATG	PBSC	Tacrolimus; MTX	3.34	D+14	D+11	Tapering of IST; Glucocorticoids; IVIG; Bortezomib	D+163	4	After 3rd doses
Chapuy *et al*[3]	72/M	MDS	MUD	A/O	RIC	PBSC	Tacrolimus; MTX	5.01	D+18	D+25	Tapering of IST; Glucocorticoids; Rituximab; Darbepoetin	D+390	6	After 1st dose
Bathini *et al*[5]	60/F	MDS	MUD	A/O	RIC	PBSC	Tacrolimus; MTX; ATG	6.0	D+11	D+18	Tapering of IST; Glucocorticoids; Rituximab; Bortezomib	D+411	4	After 1st dose
Rautenberg *et al*[4]	43/F	AML	MUD	A/O	MAC	PBSC	Tacrolimus; MMF	8.0	D+9	D+17	Tapering of IST; Rituximab	D+206	2	After 2nd dose
Salas *et al*[7]	34/M	AA	MSD	AB/O	RIC	PBSC	MTX; CSA	6.91	D+13	D+11	Tapering of IST; Rituximab; Glucocorticoids; PX; Bortezomib	D+700d	6	After 6th dose
Henig *et al*[8]	25/M	Chronic neutropenia	MSD	A/B	MAC	PBSC	MTX; CSA	7.9	D+23	D+12	Tapering of IST; Rituximab; Bortezomib	D+320	5	After 4th dose
Yates *et al*[9]	14/F	DOCK8 deficiency	Haplo	A/O	MAC	BM+PBSC	CTX; tacrolimus; MMF	9.3	D+15	D+22	Tapering of IST	D+397	3	After 3rd doses
Martino *et al*[10]	77/F	AML	NR	A/O	RIC	NR	Sirolimus tacrolimus	NR	NR	NR	NR	D+205	3	After 1st dose
Martino *et al*[10]	62/F	MDS	NR	AB/O	RIC	NR	CTX tacrolimus	NR	NR	NR	NR	D+270	2	After 2nd dose
Asawapanumas *et al*[11]	49/M	AML	MSD	B/O	MAC	NR	Pt-Cy; CSA; MMF	7.17	D+21	D+16	Tapering of IST	D+146	1	After 1st dose
Our patient	41/F	AML	MUD	AB/O	MAC	PBSC	MTX; CSA	4.67	D+11	D+12	Tapering of IST; PX; IFN; MNC	D+2701	5	After 2nd dose

M: Man; F: Female; MSD: Matched sibling donor; MUD: Matched, unrelated donor; MMF: Mycophenolat mofetil; PX: Plasma exchange; RIC: Reduced intensity conditioning; MAC: Myeloa-blative conditioning; IFN: Interferon; MNC: Mesenchymal stem cell; Haplo: Haploidentical allogeneic stem cell transplantation; DLI: Donor lymphocyte infusion; Pt-Cy: Post-transplantation cyclophosphamide; MMF: Mycophenolate mofetil; MTX: Methotrexate; CSA: Cyclosporine; CTX: Cyclophosphamide; IST: Immunosuppressive therapy.

and on day 12, platelet engraftment (31109/L) were performed. The number of neutrophils and platelets was 2.3109/L on day 14 and 112109/L on day 21. She had donor chimerism of 98.42% on day 29. Bone marrow aspiration and biopsy on day 31 post-transplant showed 45% cellularity with erythroid suppression, 36 megakaryocytes/1.5 cm × 3.0 cm, naive megakaryocytes 3%, granular megakaryocytes 45%, thrombocytogenic megakaryocytes 50%, and naked megakaryocytes 2%. Direct Coombs test was negative with reticulocytopenia (0.1%, 3000/μL), and we considered PRCA. Due to hypoplasia of the erythrocytes caused by blood incompatibility between donor and recipient, the patient relied on frequent blood transfusions, persisting over 96 d after transplantation, which resulted in secondary iron overload. The blood tests showed the concentration of serum ferritin was between 854 and 9069 ng/mL; hence, she was treated with deferasirox 1250 mg/d (20 mg/kg/d) for iron removal. She did not have any evidence of graft *vs* host disease (GVHD); therefore, cyclosporin taper was initiated on day 87 and was stopped on day 101. She continued to have reticulocytopenia and required blood transfusion every 2 weeks. The blood type identified remained O for multiple blood examinations, while the donor's type AB blood was not detected. On day 106 after transplantation, she was diagnosed with PRCA, and she failed multiple therapies for it. Glucocorticoids were started on day 124 after transplantation, and were slowly tapered over a period of several weeks. This was followed by three sessions of plasma exchange as second-line treatment on day 150, with no clinical response. From October to November 2014 (10 months after transplantation), interferon at a dose of 30 g subcutaneous injection three times a week was given without response. On day 630, 106 mesenchymal stem cells (MSCs) per 10 kg body weight was given intravenously twice weekly, and no MSC infusion-related adverse effects were noted. However, this was unsuccessful.

Personal and family history

The patient denied any family history of malignant tumours.

Physical examination

Physical examination was unremarkable.

Laboratory examinations

Bone marrow aspiration and biopsy on day 31 post-transplant showed 45% cellularity with erythroid suppression, 36 megakaryocytes/1.5 cm × 3.0 cm, naive megakaryocytes 3%, granular megakaryocytes 45%, thrombocytogenic megakaryocytes 50%, and naked megakaryocytes 2%. Direct Coombs test was negative with reticulocytopenia (0.1%, 3000/μL).

Hemoglobin 50 g/L, reticulocyte count 0.57% (17100/μL), IgM anti-A1: 128, IgG anti-A1: 512, IgM anti-B negative, IgG anti-B 1:512, 12 days after daratumumab infusion. On day 21 after daratumumab infusion: Hemoglobin 45 g/L, reticulocyte count 4.25% (127500/μL), IgM anti-A 1:64, IgG anti-A 1:128, IgM anti-B negative, and IgG anti-B 1:128, at which point the patient began to be transfusion independent. On day 28 after daratumumab infusion: Hemoglobin 60 g/L, reticulocyte count 10.37% (311100/μL), IgM anti-A1: 16, IgG anti-A1: 64, IgM anti-B negative, IgG anti-B negative, positive type O, and negative type B.

Imaging examinations

No abnormalities on imaging.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was PRCA.

TREATMENT

On July 1, 2020, we noticed a report that patients with PRCA following allo-HSCT were successfully treated with daratumumab[4]. Prior to treatment with daratumumab (on day 2694 post-transplantation), laboratory findings indicated a paucity of erythroid precursors on bone marrow examination. Erythroid elements accounted for < 1% of total cellularity. Other tests showed that the concentration of Ferritin was 4530 ng/mL, and the blood routine test showed anemia (white blood cell count 3.34 × 10^9/L, hemoglobin 37 g/L and platelet count 213 × 10^9/L). The first dose of daratumumab (16 mg/kg) was administered at day 2701 after transplantation, followed by four doss at days 2708, 2715, 2722 and 2731. We found that after a three-dose infusion of daratumumab, the patient's haemoglobin and reticulocytes began to rise and antibody titres fell, suggesting that the treatment was effective.

OUTCOME AND FOLLOW-UP

At 124 days following infusion of daratumumab, hemoglobin was 150 g/L, anti-A and anti-B were negative, and blood type was AB. In the last test, at day 3098 after transplantation: Hemoglobin 151 g/L, reticulocyte count 5.05% (151500/μL), anti-A, anti-B still negative, and blood type AB (Figures 1 and 2). A bone marrow aspirate revealed a normal number of erythroid precursors (28%) and no evidence of recurrent acute myeloid leukemia.

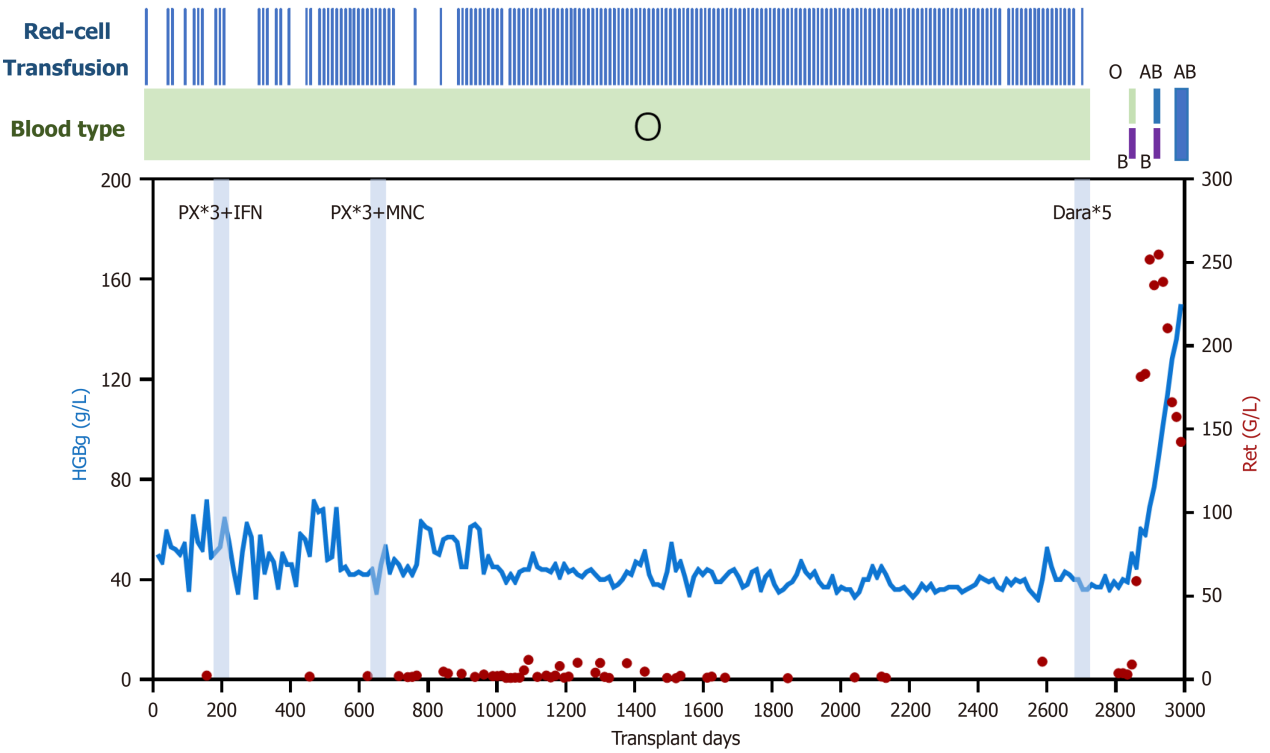


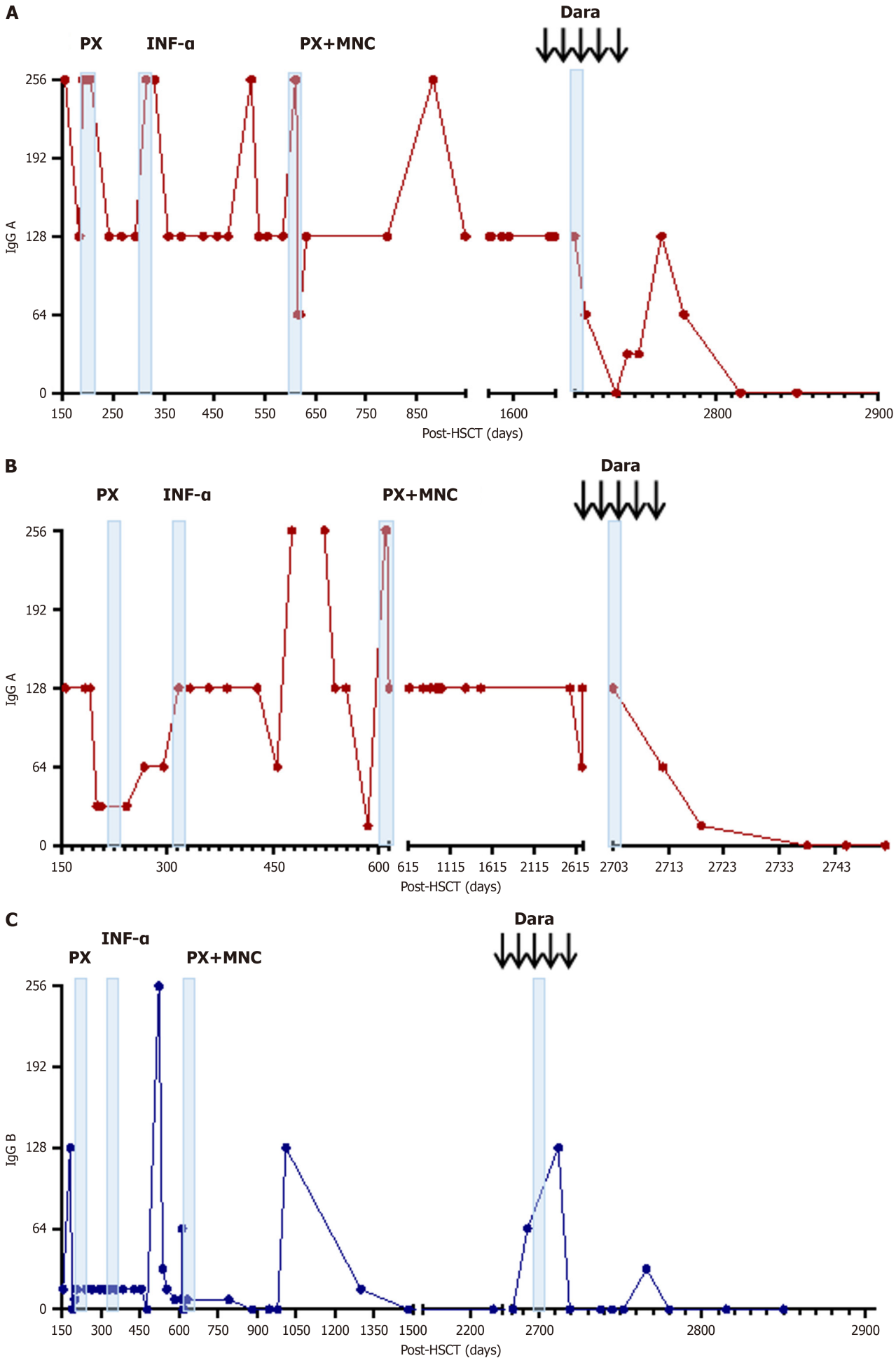
Figure 1 Treatment process of pure red cell aplastic anaemia patients after unrelated human leukocyte antigen-matched AB + /O + allo-transplantation. Hemoglobin (Y axis), transplant days (X axis), absolute value of reticulocyte, frequency of red blood cell infusion, and changes in blood type before and after transplantation are shown here, and the trend of treatment with plasmapheresis, interferon, mesenchymal stem cells, and Daratumumab (shaded) is shown. Red blood cell transfusion frequency showed no change before and after plasmapheresis, interferon, and mesenchymal stem cell treatment, but after 5 dosages of Daratumumab, hemoglobin significantly increased, red blood cell transfusion frequency decreased.

DISCUSSION

Pure red cell aplastic anemia is a complication associated with ABO mismatched allo-HSCT characterized by anemia, reticulocytopenia, and lack of erythrocytes, disregarding other causes such as infection, hemolysis, disease relapse, or drug toxicity. Since PRCA is self-limiting, it may resolve spontaneously within weeks to years. To date, there is no standard treatment for PRCA following transplantation[12]. The earliest treatments used were to taper immunosuppressants to promote graft resistance to plasma cell effects[13-15]. Yamaguchi *et al*[14] reported a case of PRCA anemia following HLA-matched HSCT, in which cyclosporine decreased by 25% every 2 weeks from day 123. Skin and liver GVHD occurred during tapering, and the patient was free from transfusion dependence at day 167. We found that nine cases reported an increase in reticulocyte count and blood transfusion independence at days 128 to 376 after transplantation using tapering of immunosuppressive therapy[13,16-18], but there were also many unsuccessful cases[19-21]. Our patient was initially treated with cyclosporine reduction, but the bone marrow erythrocytes and reticulocytes did not increase, and GVHD did not appear after tapering immunosuppressive therapy.

Corticosteroids are often used alone or in combination with other treatments, although with unsatisfactory results[22,23]. Erythropoietin (EPO) is used for PRCA to stimulate the remaining red progenitor cells in bone marrow. This effect may have resulted from the inhibition of erythropoiesis mediated by the major ABO group incompatibility, but there are fewer reports describing success of EPO therapy[24,25] compared with failure[14,26,27]. Plasma exchange is a widely used treatment, often in combination with other therapies, but is less effective in treating PRCA[28]. In patients with effective plasma exchange, initiation of therapy began > 100 d after transplantation, and > 200 d in most transfusion-dependent patients[22,29]. Donor lymphocyte infusion (DLI) treatment of PRCA after transplantation has rarely reported successful outcomes[19,28]. The donor in our case was unrelated to the patient; therefore, DLI could not be performed. The patient's bone marrow was completely chimeric with the donor during multiple examinations. DLI was not performed due to the possibility of GVHD[30]. Anti-CD20 chimeric IgG1 monoclonal antibody therapy (rituximab) is mainly used to remove the residual B lymphocytes of the host. At present, there are few successful reports on PRCA after transplantation, and the treatment course and dose are different; mostly at 375 mg/m^2, for four doses[20]. Treatment can also be 300 mg/m^2/dose[27], 235 mg/m^2/dose for four doses[31] and 150 mg/m^2/dose for three doses[27], but the practitioner should be vigilant of the risk of infection.

MSCs can significantly inhibit the proliferation, differentiation and immunoglobulin secretion of B lymphocytes, thus becoming a new treatment method for PRCA[32]. Fang *et al*[21] reported two cases of PRCA that failed with EPO and rituximab, but then received 1.5 × 106/kg donor adipose-derived MSCs at days 197 and 233 days, respectively, and achieved blood transfusion independence at days 220 and 250 days, respectively. Treatment of PRCA has also been reported sporadically with bortezomib[33-35] and Eltrombopag[36], but large-scale clinical data are lacking.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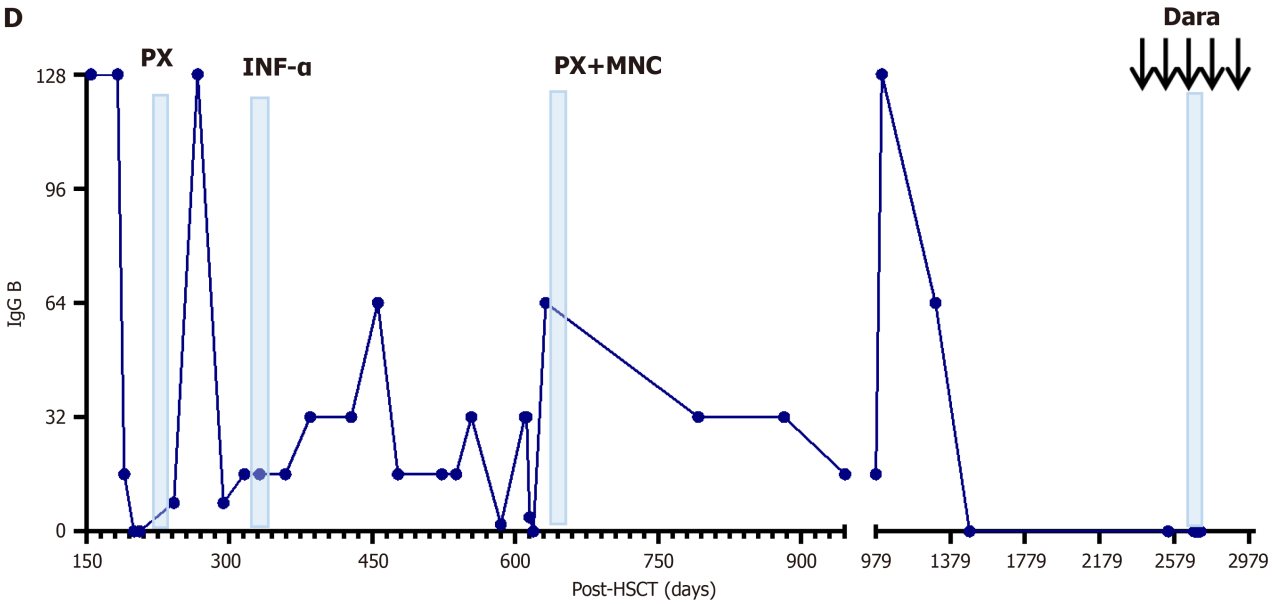

Figure 2 Changes in anti-A and anti-B titers (IgG + IgM) after transplantation. A: IgG anti-A, no significant changes in plasma exchange, interferon, and mesenchymal stem cell therapy + 1d to + 2700d after transplantation, and antibody levels gradually turned negative after Dara treatment; B: IgM anti-A, no significant changes in plasma exchange, interferon, and mesenchymal stem cell therapy until Dara treatment; C: IgG anti-B, no significant changes in plasma exchange, interferon, and mesenchymal stem cell therapy until Dara treatment; D: IgM anti-B, no significant changes in plasma exchange, interferon, and mesenchymal stem cell therapy + 1d to + 2700d after transplantation, and antibody levels gradually turned negative after Dara treatment. PX: Plasma exchange, INF: Interferon, MNC: Mesenchymal stem cell, Dara: Daratumumab.

CONCLUSION

Although there are only a few cases of PRCA treated with daratumumab, all the reported cases were cured. In addition, we noted a 74-year-old woman with a 10-year history of treatment-refractory idiopathic acquired PRCA with rapid and sustained response to daratumumab. At baseline, the patient was transfusion-dependent every 3 wk and reticulocyte percentage was < 0.28. One week after initiation of therapy, hemoglobin was > 8 g/dL and 1 and 2 mo post-therapy, hemoglobin level was 9.4 and 11 g/dL, respectively[37]. The median time of starting daratumumab varies between 146 and 700 d (median 295 d) after transplantation. Our patient received red blood cell infusion every 2 wk for > 7 years after transplantation. Due to a lack of precedence on administering daratumumab for PRCA treatments, the efficacy remained uncertain. Families of patients were fully informed of the circumstances concerning the efficacy prior to committing to the trial. The dose we used was consistent with that reported in the literature, 16 mg/kg, once a week. Antiallergic drugs were given before infusion. As the patient experienced fatigue and bone pain, the fifth dose was administered 9 d later. No serious adverse events occurred. In addition, no GVHD or opportunistic infections were observed during 397 d of follow-up after daratumumab treatment, suggestin.

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FOOTNOTES

Author contributions: Deng B and Gao R contributed to manuscript writing and editing, and data collection; Yang B, Lei WB, Xue MF contributed to data analysis; Wang JS performed the treatment; Zhao P contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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CASE REPORT

Splenic subcapsular hematoma following endoscopic retrograde cholangiopancreatography: A case report and review of literature

Chen-Yu Guo, Yu-Xia Wei

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Abstract

BACKGROUND

Splenic injury following endoscopic retrograde cholangiopancreatography (ERCP) is a rare complication. The literature contains around 30 articles reporting various degrees of splenic injuries resulting from ERCP since the first report of splenic rupture after ERCP in 1989.

CASE SUMMARY

This report describes a case of splenic hematoma and stent displacement in a 69-year-old male patient who developed these conditions 7 days after undergoing ERCP and stenting. The patient had bile duct stenosis caused by a malignant tumor that was obstructing the bile duct. The diagnosis was confirmed by epigastric computed tomography and magnetic resonance cholangiopancreatography. The patient was successfully treated with percutaneous transhepatic cholangial drainage, endoscopic pyloric stent placement, and conservative management. The causes of splenic injury following ERCP are discussed.

CONCLUSION

ERCP has the potential to cause splenic injury. If a patient experiences symptoms such as abdominal pain, decreased blood pressure, and altered hematology after the procedure, it's important to be thoroughly investigated for postoperative bleeding and splenic injury.

Key Words: Endoscopic retrograde cholangiopancreatography; Gastroenterology; Splenic injury; Hematoma; Case report

Core Tip: There are several possible causes of abdominal pain and fever in patients who have undergone endoscopic retrograde cholangiopancreatography (ERCP). One of the potential complications that should not be overlooked is splenic injury. A clear diagnosis can be established based on laboratory and imaging examinations. It is important to closely monitor the patient's condition after ERCP and to promptly address any signs of discomfort.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a frequently used diagnostic and therapeutic tool for pancreatobiliary disease[1]. Complications occur in 5%-10% of cases and may include pancreatitis, bleeding, and perforation[2]. Although rare, splenic injury has also been reported following ERCP. Our literature review found approximately 30 reported cases of splenic injury since the first case was reported in 1989[3]. Details of the first report and subsequent similar reports are shown in Table 1[3-30]. We describe a patient who developed a splenic hematoma after undergoing ERCP. The diagnosis was confirmed by objective imaging, and the condition was successfully treated using conservative methods.

CASE PRESENTATION

Chief complaints

A 69-year-old male patient presented to our clinic with complaints of jaundice, accompanied by nausea, lower abdominal distension, and pain.

History of present illness

The patient's symptoms started 1 week ago with no apparent trigger.

History of past illness

Three years ago, the patient was diagnosed with multiple tumors of the sigmoid colon and underwent laparoscopic sigmoidectomy. Pathology revealed multiple malignant tumors of the sigmoid colon. The patient subsequently underwent conventional chemotherapy.

One year ago, the patient exhibited occupying lesions in the intrahepatic bile ducts of the left outer lobe of the liver near the hepatic hilum. The patient subsequently underwent a left lobe hepatectomy and cholecystectomy.

Personal and family history

The patient reported no family history of malignant tumors and no history of smoking or drinking.

Physical examination

The patient's vital signs were as follows: Body temperature, 36.5 °C; heart rate, 80 bpm; respiratory rate, 20 breaths/min; and blood pressure, 103/77 mmHg. Additionally, there was a visible postoperative scar in the anterior midline of the abdomen, as well as abdominal and epigastric tenderness.

Laboratory examinations

Admission liver function tests showed the following: Alanine aminotransferase (ALT) 424.4 U/L, aspartate transaminase (AST) 210.9 U/L, glutamyl transferase (GGT) 1096 U/L, alkaline phosphatase (ALP) 259 U/L, total bilirubin 130.91 μmo1/L, direct bilirubin 71.71 μmol/L, and indirect bilirubin 59.2 μmol/L.

Imaging examinations

Abdominal ultrasound showed dilatation of the bile ducts in the liver. The duodenum was not peristaltic and metastasis was suspected in the duodenum and its periphery in the hepatic portal position.

Admission magnetic resonance cholangiopancreatography (MRCP) (Figure 1A) showed narrowing of the right hepatic duct was at the porta hepatis, which corresponded to a dilation of the intrahepatic bile duct in the right lobe of the liver. No dilatation or narrowing of the common hepatic duct or common bile duct was observed.

Table 1 Published reports on spleen injuries worldwide following endoscopic retrograde cholangiopancreatography

Ref.	Year	Age/gender	Comorbid conditions	Clinical manifestations	Onset after ERCP	Type of injury	Therapy
Trondsen *et al*[3]	1989	46/Female	Pancreatitis	ERCP, sphincterotomy	15 hours	Splenic capsular avulsion	Splenectomy
Pamudurthy *et al*[4]	2018	60/Female	Choledocholithiasis	ERCP, stenting	8 hours	Splenic rupture	Splenectomy
Grammatopoulos *et al*[5]	2014	64/Male	Obstructive jaundice, tumor	ERCP, stenting	6 hours	Splenic rupture	Splenectomy
Boustany *et al*[6]	2023	41/Female	Gallstone pancreatitis, cholecystectomy	ERCP, stenting	24 hours	Splenic subcapsular hematoma	Embolization
Polman *et al*[7]	2020	52/Male	Nil	ERCP, stenting	Immediately	Splenic laceration	Embolization
Montenovo *et al*[8]	2017	41/Female	Liver transplant	ERCP, sphincterotomy	8 hours	Splenic subcapsular hematoma	Splenectomy
Momani *et al*[9]	2018	44/Female	Sleeve gastrectomy	ERCP, sphincterotomy	A few hours	Splenic subcapsular hematoma	Conservative
Haneke *et al*[10]	2018	39/Male	Chronic pancreatitis	ERCP	6 days	Splenic abscess	Conservative
Lee *et al*[11]	2017	59/Female	Profound jaundice.	ERCP, replace stenting	4 hours	Peri-splenic hematoma	Conservative
Cebrián García *et al*[12]	2022	83/Male	Nil	ERCP, sphincterotomy	6 hours	Splenic rupture	Splenectomy
Lubikowski *et al*[13]	2020	31/Female	Hepatectomy, biliary leak	ERCP, stenting	Shortly	Splenic rupture	Splenectomy
Agarwal *et al*[14]	2022	63/Male	Jaundice	ERCP, sphincterotomy, stricturoplasty, stenting	4 days	Splenic hematoma	Embolization
Kingsley *et al*[15]	2001	54/Female	Chronic pancreatitis, hepatitis C, cirrhosis	ERCP, sent revision	24 hours	Splenic rupture	Splenectomy
Badaoui *et al*[16]	2002	42/Male	Cholecystolithiasis, Common bile duct dilation	ERCP	20 minutes	Splenic laceration	Conservative, surgery
Lewis *et al*[17]	1991	49/Female	Common bile duct stricture, pancreatic head tumor	ERCP, stenting, biopsy	9 hours	Avulsion of short gastric vessels	Splenectomy
Ong *et al*[18]	1991	55/Female	Common bile duct stricture, tumor	ERCP	48 hours	Intrasplenic hematoma	Splenectomy
Furman *et al*[19]	1993	63/Female	Common bile duct stricture	ERCP, papillotomy	Not reported	Splenic subcapsular hematoma; Splenic abscess, pancreatitis	Observation, abscess drained
Wu *et al*[20]	1993	57/Female	Pelvic surgery	ERCP, sphincterotomy	60 hours	Splenic capsular avulsion	Splenectomy
Lo *et al*[21]	1994	79/Male	Billroth I anastomosis	ERCP, papillotomy	48 hours	Splenic subcapsular hematoma	Observation,
Deist *et al*[22]	2003	52/Female	Prior abdominal surgery	ERCP, sphincterotomy	8 hours	Splenic rupture	Splenectomy
Zyromski *et al*[23]	2004	33/Female	Nil	ERCP, sphincterotomy	24 hours	Avulsion of short gastric vessels	Splenectomy
Dixon *et al*[24]	2004	38/Male	Chronic pancreatitis	ERCP	Immediately	Splenic capsular avulsion	Laparotomy
Cho *et al*[25]	2008	63/Female	Prior laparotomy	ERCP	18 hours	Splenic laceration	Splenectomy
Cortiñas Sáenz *et al*[26]	2010	82/Female	Cardiovascular disease	ERCP	Immediately	Splenic rupture	Splenectomy
Gaffney *et al*[27]	2012	48/Female	Common bile duct dilation, Chronic pancreatitis	ERCP, replace stent	6 days	Splenic subcapsular hematoma	Conservative
Paredes *et al*[28]	2013	39/Female	Cholecystectomy, adherent omentum	ERCP, sphincterotomy, stenting	1 hour	Splenic laceration	Splenectomy

Weaver *et al*[29]	2014	66/Male	Choledocholithiasis	ERCP	Overnight	Splenic subcapsular hematoma	Splenectomy
Ahmad *et al*[30]	2016	76/Male	Choledocholithiasis	ERCP, sphincterotomy	30 minutes	Splenic capsular avulsion	Splenectomy

ERCP: Endoscopic retrograde cholangiopancreatography.

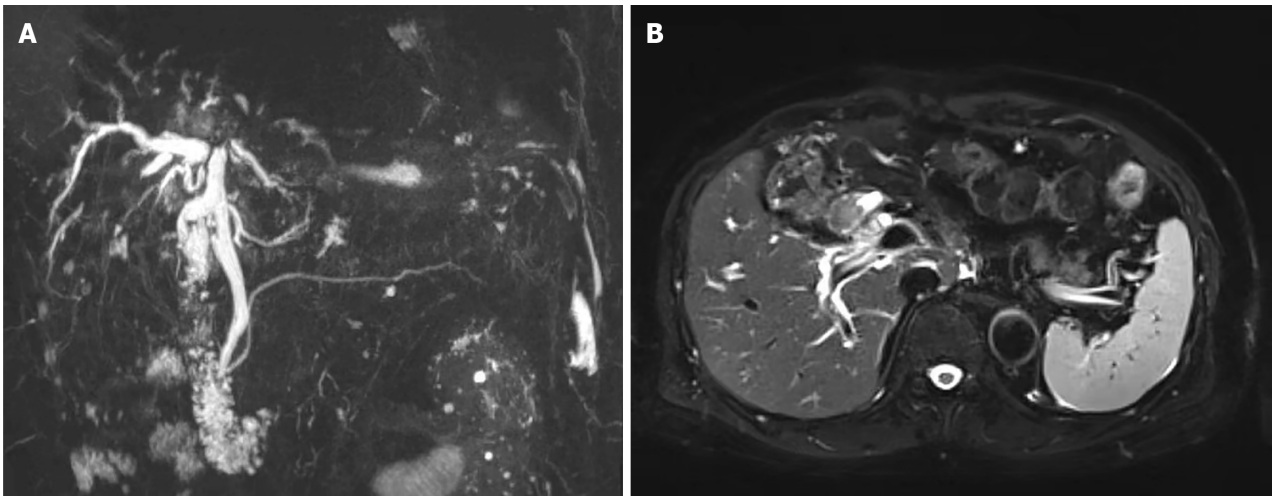

Figure 1 Admission magnetic resonance cholangiopancreatography and magnetic resonance imaging. A: Magnetic resonance cholangiopancreatography revealed a narrowing of the right hepatic duct at the porta hepatis; B: The spleen is morphologically normal with a homogeneous parenchymal signal.

Admission magnetic resonance imaging (MRI) of the upper abdomen (Figure 1B) revealed that the spleen was morphologically normal with a homogeneous parenchymal signal. Postoperative changes were observed in the liver and gallbladder. Additionally, there was limited stenosis of the right hepatic duct in the hilar region.

FINAL DIAGNOSIS

The patient was diagnosed with obstructive jaundice, liver tumor (metastasis of colon cancer), and liver insufficiency.

TREATMENT

In conjunction with the expert opinions of other hospitals, to ensure smooth bile drainage and prevent liver failure, the patient underwent ERCP and stent implantation 1 week after admission in our hospital. During the ERCP procedure, the lateral scope was passed smoothly under intravenous anesthesia in the prone position. The esophageal cardia entered the gastric cavity and it was difficult to pass the scope through the pylorus; thus, the anterior scope was replaced by a guide wire which was placed through the pylorus into the jejunum, and then the lateral scope was replaced by inserting a balloon through the guide wire, and repeated attempts were made to enter the descending portion of the duodenum. The balloon guidewire was removed and the main papilla was found on the medial side of the descending portion, which showed a papillary shape with a granular opening. The bile duct was difficult to intubate, the pancreatic duct was accessed, a pancreatic duct guide wire was left in place and the bile duct was visualized by re-accessing the bile duct and administration of contrast into the bile duct. The contrast agent used was iodixanol. The X-ray showed: Bile duct stenosis in the porta hepatis, dilatation of the left hepatic duct, and the right hepatic duct was not visualized. As the bile duct was difficult to intubate, the guidewire was repeatedly entered into the pancreatic duct several times, and in order to prevent ERCP pancreatitis, the papilla was incised to 0.4 cm with an incision knife and a pancreatic stent of 5F diameter and 5 cm length was placed through the pancreatic duct guidewire and pancreatic fluid was seen to drain. After placing an 8.5F diameter, 11cm long unilateral plastic wing stent through the bile duct guidewire, bile was seen to flow out and the operation was completed. Liver function test 24 hours after ERCP revealed ALT 175 U/L, AST 87 U/L, GGT 565 U/L, ALP 142 U/L, total bilirubin 83.9 μmo1/L, direct bilirubin 60.4 μmol/L, and indirect bilirubin 15.8 μmol/L. These indices had significantly improved compared to the previous values.

OUTCOME AND FOLLOW-UP

On the 7th day after ERCP, the patient had worsening abdominal pain, fever (38.7 °C), poor mental status, nausea, and vomiting, and a hematoma was seen under the palpated splenic hilum on computed tomography (CT) (Figure 2) and MRCP (Figure 3) of the upper abdomen, but the etiology of the disease was not yet clarified. In addition, biliary stent displacement and poor bile drainage were observed. Liver function tests showed an upward trend, and 7 days after ERCP liver function showed the following: ALT 134 U/L, AST 107 U/L, GGT 658 U/L, ALP 212 U/L, total bilirubin 126.8 μmo1/L, direct bilirubin 100.2 μmol/L and indirect bilirubin 26.6 μmol/L. Percutaneous hepatic puncture biliary drainage (PTCD) was performed, resulting in good drainage and the patient's jaundice gradually subsided. Abdominal pain and other symptoms significantly improved two days later.

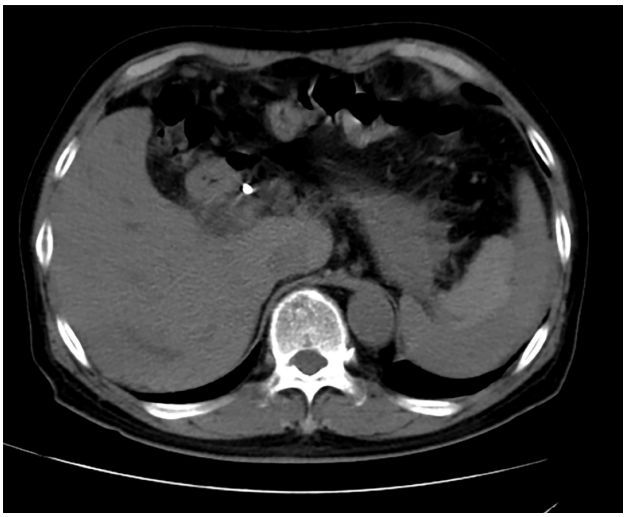

Figure 2 Computed tomography scan revealed a hematoma in the spleen after endoscopic retrograde cholangiopancreatography.

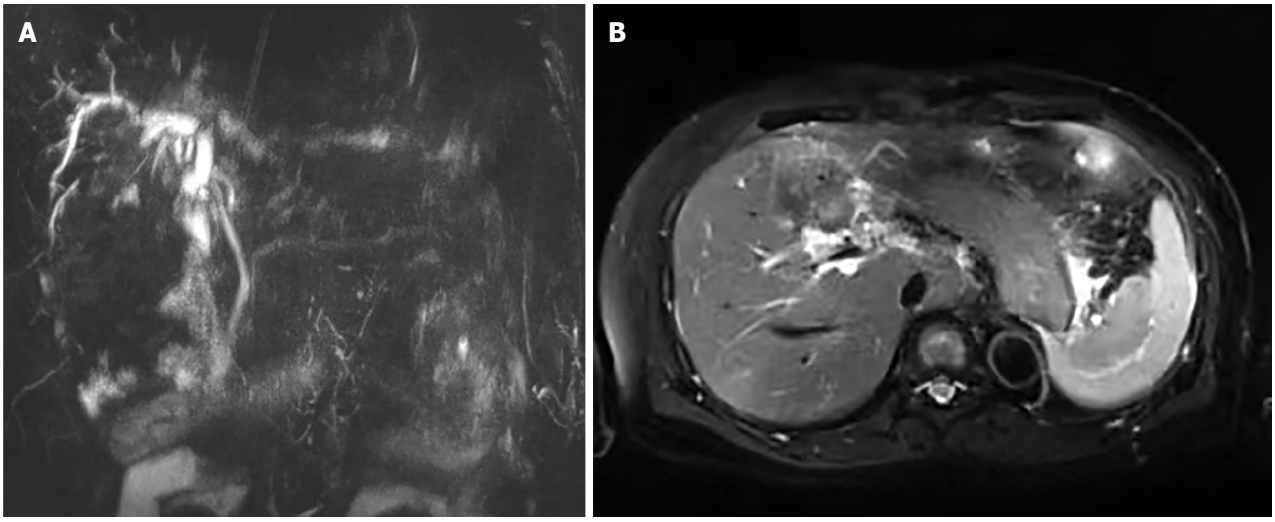

Figure 3 Magnetic resonance cholangiopancreatography and magnetic resonance imaging after endoscopic retrograde cholangiopancreatography. A: Biliary and pancreatic stents can be visualized and stent migration was considered based on the patient's elevated liver function; B: Magnetic resonance imaging revealed a hematoma in the spleen.

Twelve days after PTCD, the patient had no obvious discomfort. We planned to perform ERCP again to reposition the stent, remove the PTCD drain, and achieve intrahepatic biliary drainage. During the operation, a large mass was observed on the posterior wall of the gastric sinus and the greater curvature of the external pressure side. This caused a narrowing of the gastric sinus lumen and severe deformation of the pylorus, making it impossible to pass an endoscope. To address this, the operation mode was changed and endoscopic pyloric stent placement was performed (Figure 4). The stent was successfully positioned.

The patient's abdominal CT was reviewed 3 days before discharge (Figure 5), and the splenic hematoma had resolved. Subsequently, the patient attended our hospital every 3 months to have the PTCD drain changed and received radio-

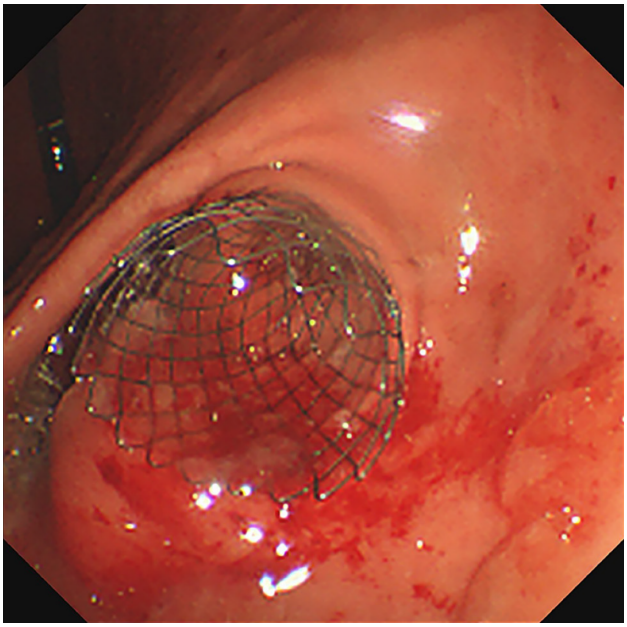

Figure 4 Endoscopic pyloric stent placement with minor intraoperative bleeding.

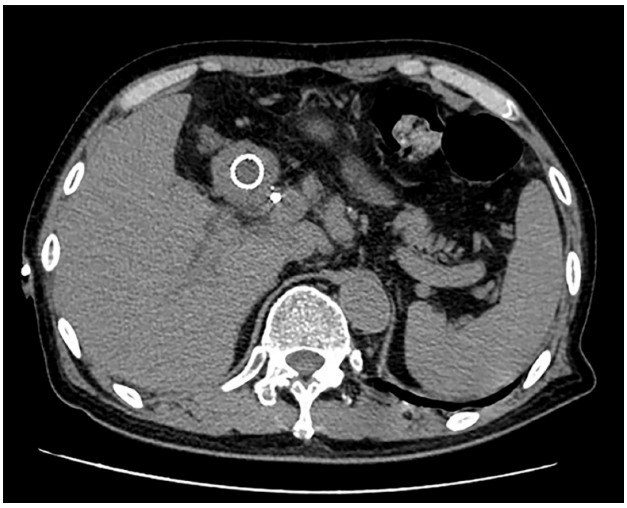

Figure 5 A computed tomography scan conducted before discharge showed that the splenic hematoma had disappeared.

therapy at the same time, The patient's abdominal CT was reviewed several times during the year, and the splenic morphology was normal.

DISCUSSION

ERCP is a vital tool for diagnosing and treating pancreatic and bile duct diseases. In this case, a tumor in the hepatic hilum was compressing the bile duct, causing obstructive jaundice. Stent placement *via* ERCP provided a palliative intervention. Postoperative complications, such as pancreatitis, perforation, and hemorrhage, are common[31,32]. Rare complications have also been reported internationally, such as death caused by air embolism[33], duodenal perforation due to biliary stent displacement[34], and hepatic hematoma[35]. It is important to note that these complications are infrequent. Splenic injuries include splenic subcapsular hematoma, splenic hematoma, splenic capsular avulsion, perisplenic hematoma, intrasplenic hematoma, splenic laceration, splenic rupture, splenic abscess, and short gastric vessel avulsion.

The risk factors for splenic injury after previous ERCP include calcification and fibrosis of the supporting ligaments, such as the splenocolic and gastrosplenic ligaments, which can cause decreased mobility of the viscera. These risk factors are particularly relevant for patients with cirrhosis and chronic pancreatitis. Excessive traction on the ligaments can result in splenic injury[4]. Abdominal adhesions can also develop after abdominal surgery[5,6]. If a patient experiences abdominal pain, decreased blood pressure or hematocrit, and hemodynamic instability after ERCP, it is important to

consider the possibility of splenic injury[7,8]. Depending on the severity of the injury, conservative management[9,10,11], splenectomy[8,12,13], or splenic artery embolization[6,7,14] may be employed to control bleeding after a splenic injury.

Our patient had stenosis of the pylorus and bile ducts due to compression by a hepatic tumor. The endoscope caused excessive traction or shear force when passing through the pylorus and bile ducts, which caused the greater curvature of the stomach to twist and led to splenic injury following excessive traction of the splenic colonic ligament. The patient underwent two major abdominal surgeries, including a left lobe hepatectomy and cholecystectomy. These procedures may have resulted in calcification of the peri-splenic ligament and vascular adhesions, which ultimately contributed to the splenic injury. The clinical symptoms of both biliary stent displacement and splenic haematoma can manifest as abdominal pain and fever, so the symptoms of patient on day 7 after ERCP may have been caused by both of these conditions. Stent displacement can be caused by excessive external compression or oblique vectorial compression resulting from a change in position. This reporte indicates that there is no correlation between stent displacement and splenic hematoma, suggesting that the latter does not cause stent displacement.

CONCLUSION

Splenic injury is a rare complication of ERCP that requires attention. The onset of symptoms can occur rapidly, within minutes, or may be delayed for up to a week. The severity and type of injury may also vary. Therefore, it is essential to be vigilant, conduct a careful investigation, and appropriately treat or manage patients who present with symptoms after ERCP to treat such complications.

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FOOTNOTES

Author contributions: Guo CY collected clinical data on patients, searched for similar published cases, and wrote the paper; Wei YX designed the study, participated in endoscopic retrograde cholangiopancreatography, and supervised the writing of the paper. Both authors have read and approved the final manuscript.

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CASE REPORT

"Keyboard sign" and "coffee bean sign" in the prenatal diagnosis of ileal atresia: A case report

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Abstract

BACKGROUND

Ileal atresia is a congenital abnormality where there is significant stenosis or complete absence of a portion of the ileum. The overall diagnostic accuracy of prenatal ultrasound in detecting jejunal and ileal atresia is low. We report a case of ileal atresia diagnosed prenatally by ultrasound examination with the "keyboard sign" and "coffee bean sign".

CASE SUMMARY

We report a case of ileal atresia diagnosed in utero at 31 weeks' of gestation. Prenatal ultrasound examination revealed two rows of intestines arranged in an 'S' shape in the middle abdomen. The inner diameters were 1.7 cm and 1.6 cm, respectively. A typical "keyboard sign" was observed. The intestine canal behind the "keyboard sign" showed an irregular strong echo. There was no normal intestinal wall structure, showing a typical "coffee bean sign". Termination of the pregnancy and autopsy findings confirmed the diagnosis.

CONCLUSION

The prenatal diagnosis of ileal atresia is difficult. The sonographic features of the "keyboard sign" and "coffee bean sign" are helpful in diagnosing the location of congenital jejunal and ileal atresia.

Key Words: Ileal atresia; The prenatal diagnosis; Keyboard sign; Coffee bean sign

Core Tip: The prenatal diagnosis of ileal atresia is difficult. The sonographic features of “keyboard sign” and “coffee bean sign” are helpful to diagnose the location of congenital jejunal and ileal atresia.

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INTRODUCTION

Small bowel atresia is a congenital obstruction of the lumen of the duodenum, jejunum or ileum. Small bowel atresia is one of the most common causes of congenital bowel obstruction, with an incidence between 0.57 and 6.6 per 10000 Live births[1,2]. The pathophysiology of small bowel atresia has not yet been completely elucidated[3]. The most accredited hypothesis relates to an early mesenteric vascular accident leading to ischemia and obliteration of the intestinal lumen[4].

Although mortality due to small bowel atresia is low, especially in isolated cases, newborns with small bowel atresia are still affected by significant morbidities such as sepsis, short bowel syndrome and a need for prolonged total parenteral nutrition and hospital stay[1,5].

While duodenal atresia is commonly detected prenatally by the presence of the “double-bubble” sign, antenatal detection of jejunal and ileal atresia remains challenging[2]. The diagnostic accuracy of jejunal and ileal atresia has been reported to vary between 25% and 50%[6].

The detection rate of jejunal and ileal atresia by ultrasound has not improved in the last decade, thus highlighting the lack of standard prenatal ultrasound signs for the diagnosis of jejunal and ileal atresia and the need for further studies to define them[1]. We report a case of ileal atresia diagnosed prenatally by ultrasound examination with the “keyboard sign” and “coffee bean sign”.

CASE PRESENTATION

Chief complaints

A 26-year-old woman gravida 1, para 0, with a slightly wider colon was referred to our prenatal diagnosis center at 31 weeks' of gestation.

History of present illness

At 22 weeks of pregnancy, during the first prenatal ultrasound screening, the intestinal diameter of the pregnant woman was normal. However, at 32 weeks of gestation, a follow-up ultrasound examination revealed an increase in intestinal diameter.

History of past illness

Maternal history included no smoking, alcohol consumption, or any known teratogenic exposure.

Personal and family history

Physical examination here was no other medical or surgical history, no family history, and no consanguinity.

Physical examination

The general condition of the woman was good, no edema.

Laboratory examinations

A low risk for Down's screening, Torch test negative.

Imaging examinations

Prenatal sonography showed that the amniotic index was 9.9 cm. There were no abnormalities in the gastric bubble. The duodenum was not dilated. In the middle abdomen of the fetus, there were two rows of intestines arranged in an ‘S’ shape in parallel (Figure 1), with an inner diameter of 1.2 cm and good sound transmission. The echo of the intestinal wall was similar to that of bone. Continuous scanning of the cross-section showed that there was a ‘C’ shape of intestine in the middle and lower abdomen, with an inner diameter of 1.4 cm. The sound inside was Intestinal turbidity. The echo of the intestinal wall was normal. Scanning upward from the anus revealed that the rectum was approximately 0.9 cm wide, the sigmoid colon was 0.7 cm, and the empty structure of the remaining colon was unclear. After 30 minutes, a second examination showed that the size of the gastric bubble was normal, and the duodenum did not dilate. Only a row of intestinal canal was seen horizontally arranged in the middle abdomen (Figure 2). The inner diameter of the intestine

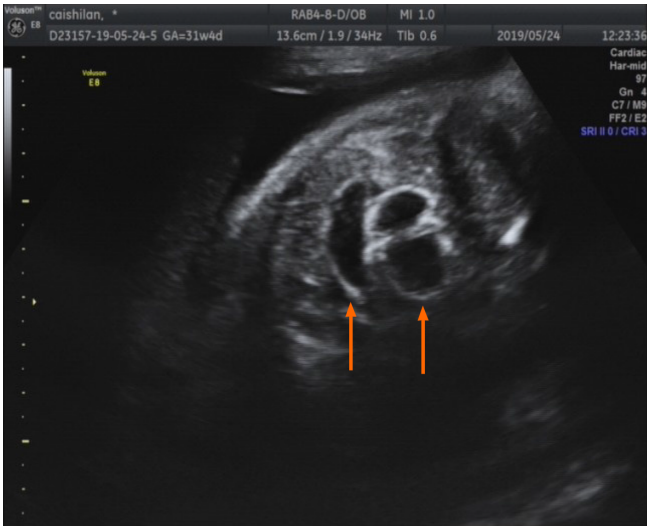

Figure 1 Ultrasound findings. Two rows of intestines arranged in an "S" shape in parallel in the middle abdomen of the fetus (arrows).

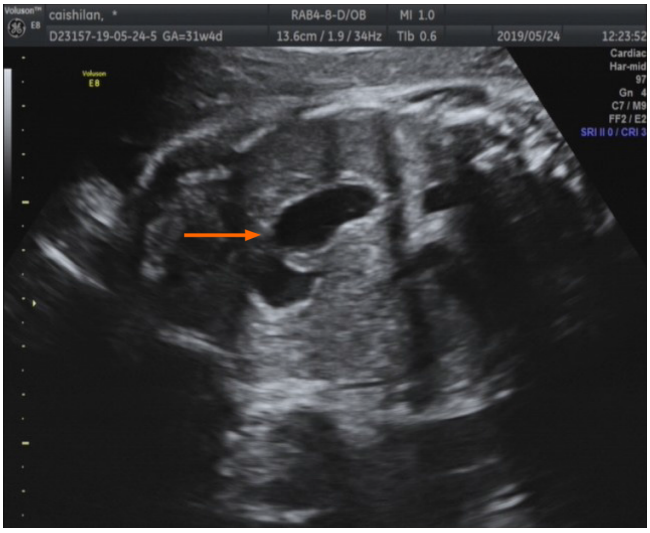

Figure 2 Subsequent ultrasound findings. After 30 minutes, only a row of intestinal canal was seen horizontally arranged in the middle abdomen (arrow).

canal was 1.1 cm, and the sound transmission was good. Three hours later, re-examination showed that there were two rows of intestines arranged in an "S" shape in the middle abdomen. The inner diameters were 1.7 cm and 1.6 cm, respectively.

The intestinal tract was significantly dilated, and the intestinal wall resembled piano keys. It showed a typical "keyboard sign". This was different to the ultrasound features of apple pear intestinal atresia in type IIIb jejunal obstruction, which has a poor diagnosis due to its association with mid gut volvulus leading to long segment bowel loss[7]. The proximal "keyboard sign" was dense and neat, while the distal "keyboard sign" was sparse and irregular (Figure 3). The intestine canal behind the "keyboard sign" showed an irregular strong echo. There was no normal intestinal wall structure, showing a typical "coffee bean sign"[8]. There was no blood flow signal in the strong echo intestinal canal. The internal low echo of the "coffee bean sign" was mesentery with a blood flow signal (Figure 4).

FINAL DIAGNOSIS

Type II ileal atresia.

TREATMENT

After thorough genetic eugenics consultation, the woman chose an induced abortion and agreed to an autopsy.

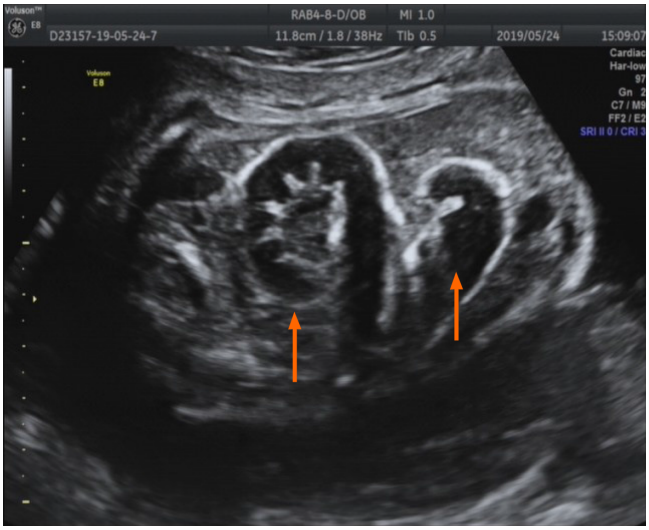

Figure 3 Keyboard sign. The proximal "keyboard sign" was dense and neat (left arrow), while the distal "keyboard sign" was sparse and irregular (right arrow).

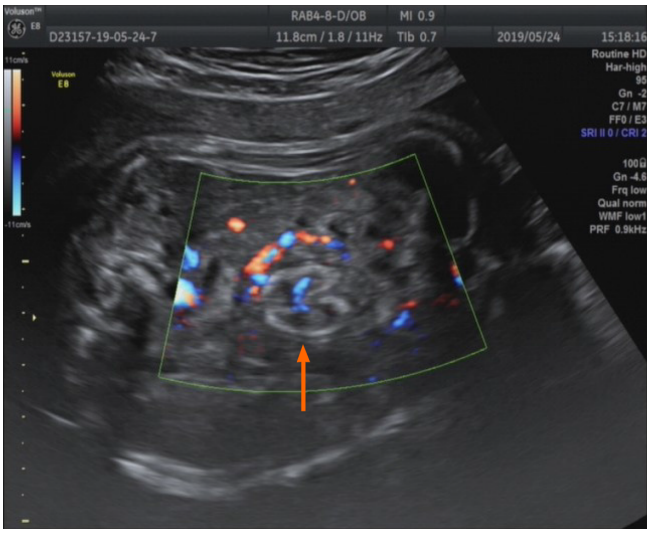

Figure 4 Coffee bean sign. The internal low echo of the "coffee bean sign" was mesentery with a blood flow signal (arrow).

OUTCOME AND FOLLOW-UP

The woman was counseled accordingly and she elected to have the pregnancy terminated. Autopsy examination confirmed the prenatal diagnosis of ileal atresia. It was observed that the dilated jejunal canal was full of feces (Figure 5A). The inner diameter of the widest part was approximately 2.3 cm. There was a small amount of green feces in the rectum. The sigmoid colon, descending colon, transverse colon and ascending colon were normal, with no feces. The cecum and appendix had returned to their normal position. Part of the descending colon had a nodular appearance. There was partial atresia in the upper ileum. Both ends were blind. The upper part of the atresia canal was dilated. The expanded inner diameter was about 2.3 cm. The mesentery was intact. There was a thin fibrous band connecting the two blind ends. The structure of the intestinal wall was normal in the proximal ileal atresia. The distal ileal atresia end was distorted showing the "coffee bean sign", white in appearance and hard in texture (Figure 5B). In addition, there was no normal intestinal wall and lumen. There was white sticky paste in the intestine. No obvious abnormalities were found in the stomach and duodenum. The diagnosis was type II ileal atresia.

DISCUSSION

Small bowel atresia can occur anywhere throughout the small intestine, with approximately 54% in the jejunum and 43% in the ileum[3]. Small bowel atresia can be classified into 4 types. Type I atresia is caused by a luminal diaphragm with a continuing outer muscular layer. In type II, the two blind ends of the bowel are attached by a fibrous cord. Type III atresia is complete separation of the bowel ends. Our case had type II ileal atresia[3,9,10]. The accuracy of prenatal ultrasound

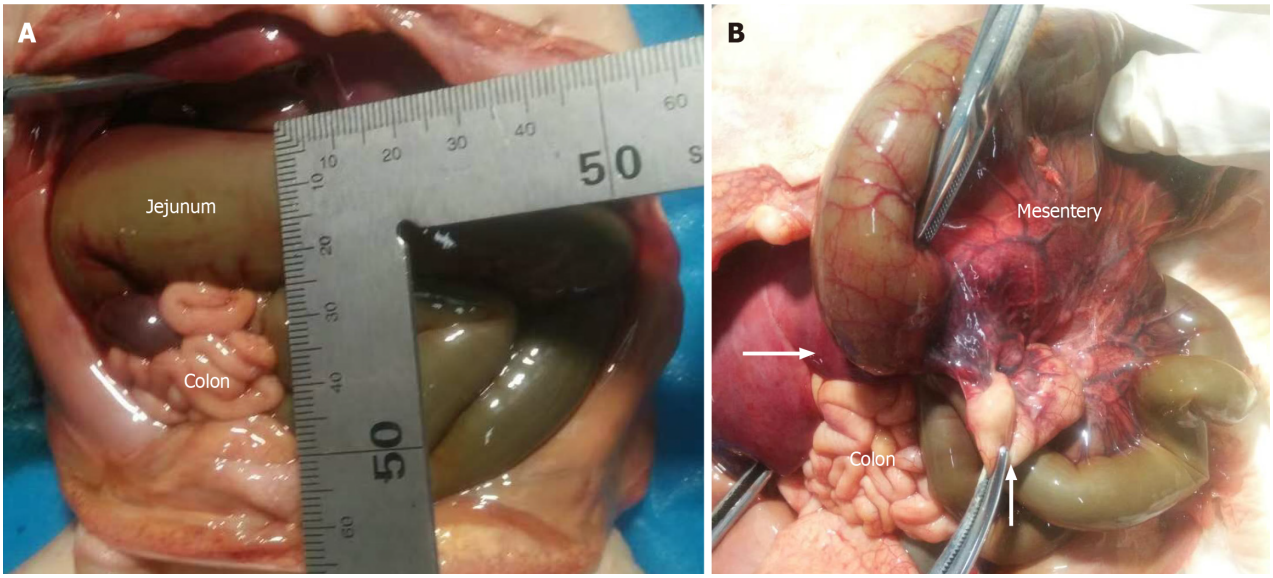

Figure 5 Autopsy findings. A: Dilated jejunum, small colon; B: Ileal atresia, the proximal blind end (left arrow). The distal blind end, with the "coffee bean sign" (right arrow).

examination in detecting jejunal and ileal atresia is reported in the literature to be highly variable[11]. However, we accurately judged our case of ileal atresia based on the ultrasound image features of the "keyboard sign" and "coffee bean sign".

In 1979, scholars found that expansion of the jejunum would show the "keyboard sign"[12]. The discovery of the "keyboard sign" requires significant clinical experience[13]. In recent years, there have been few reports on the "keyboard sign", as sonographic demonstration of this sign is difficult. In this case, the typical "keyboard sign" appeared for only 5 min, as the shape and position of the intestine were constantly changing. The dilated intestine arranged laterally in the middle abdomen was easily mistaken for the transverse colon. In addition, the "C" shaped dilated bowel in the lower abdomen was easily mistaken for the ascending or descending colon. On the contrary, anatomical results often showed that the expanded jejunum and ileum occupied the whole abdominal cavity. The adjacent colon was small and curly. In order to reduce misdiagnosis, we cannot just identify the intestinal canal by location during ultrasound examination. Instead, the digestive tract should be scanned in sequence.

The position and shape of small intestine distention were changeable due to peristalsis. The dilated small intestine often fills the whole abdominal cavity, which makes the empty colon difficult to display. The distended colon was located in the periphery without obvious peristalsis. The position of the hepatic flexure and the splenic flexure were relatively fixed. The sigmoid colon in the oblique coronal section of the lower abdomen was S-shaped.

Although there was no obvious boundary between the jejunum and ileum, there were differences in the structure of the intestinal wall. The annular plica of jejunum mucosa was greater and higher, with more and higher villi. The villi gradually decreased to the distal end and became longitudinal plica up to the end of the ileum[14]. The structural difference between the jejunum and ileum made the expansion of the jejunum form a typical "keyboard sign", while the "keyboard sign" in the ileum was not obvious.

In our case, there were two different characteristics of the "keyboard sign". The reasons for this are as follows: The "keyboard sign" in the proximal part of the intestine was regular, while that in the distal part was rare and irregular. This was considered to be caused by different positions of the intestine. The "keyboard sign" in the proximal part was due to jejunum expansion, and that in the distal part was located at the jejunum ileum junction or formed by ileum expansion. The ultrasonographic features of the "keyboard sign" only appeared for 5 min, which was considered to be related to pressure of the intestinal fluid. Only when a large amount of intestinal fluid accumulates to form a certain pressure can the "keyboard sign" be formed[12,13]. When the pressure decreased after peristalsis, the "keyboard sign" disappeared or failed to form.

In our patient, there was a strong echo due to the "coffee bean sign" located under the "keyboard sign". The echo was similar to that of bone. We considered that this was due to the decrease in fluid content in the wall of the intestine and cystic fibrosis of the intestinal wall. The presence of the "coffee bean sign" was caused by intestinal atresia. The intestine was discontinuous and distorted. Therefore, according to the strong echo "coffee bean sign", we considered that this was the closed ileum. Ileal atresia was confirmed after delivery.

CONCLUSION

Most cases of intestinal obstruction are not apparent until the third trimester and the sonographic features are not unique. It is necessary to pay attention to the characteristics of the intestine, especially the typical ultrasound image characteristics. The sonographic features of the "keyboard sign" and "coffee bean sign" are helpful in diagnosing the location of

congenital jejunal and ileal atresia.

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FOOTNOTES

Author contributions: Yin C, Fei ZH and Zhou QY were responsible for writing the manuscript; Zhou QY and Fan L collected the patient data; The surgery was performed by Yin C and Fei ZH; All authors have read and approved the final manuscript.

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CASE REPORT

Treatment of nasopharyngeal carcinoma and prevention of non-alcoholic Wernicke's disease: A case report and review of literature

Yu-Yang Ma, Xiao-Chan He, Yu Gao, Tian-Tian Ma, Gong Cheng, Chang-Wu Yue

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Abstract

BACKGROUND

Wernicke encephalopathy is a neurological disorder caused by thiamine deficiency, commonly seen in alcoholic populations but also involving other circumstances that may lead to thiamine deficiency. The recognition of Wernicke encephalopathy often depends on clinicians' keen ability to detect its typical triad of features; however, most cases do not present with the full constellation of signs, which complicates the timely identification of Wernicke encephalopathy.

CASE SUMMARY

This case report describes a patient with nasopharyngeal carcinoma who developed abnormal ocular function and ataxia following concurrent chemoradiotherapy, without a history of alcohol abuse. With the aid of radiological examinations, he received a timely diagnosis and treatment; however, his symptoms did not fully resolve during follow-up.

CONCLUSION

For patients with malignant tumors exhibiting neurological symptoms, clinicians should consider the possibility of Wernicke encephalopathy and provide prophylactic thiamine therapy.

Key Words: Nasopharyngeal carcinoma; Non-alcoholic Wernicke's disease; Wernicke's encephalopathy; Neurological; Case report

Core Tip: Following concurrent chemoradiotherapy in a patient with nasopharyngeal carcinoma, we diagnosed a case of Wernicke's encephalopathy. This article further outlines the current diagnostic techniques for Wernicke encephalopathy and the latest advancements in retrospective studies related to Wernicke encephalopathy. This finding provides a new perspective for research on the diagnosis and preventive measures of Wernicke encephalopathy associated with head and neck malignancies.

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INTRODUCTION

Wernicke's encephalopathy (WE) is a severe neurological disorder caused by thiamine (vitamin B1) deficiency, characterized primarily by the classic triad of mental status changes, ocular dysfunction, and ataxic gait. However, only a minority of cases present with the complete triad[1], which undoubtedly affects the timely diagnosis of the disease. The onset of WE is often associated with excessive alcohol intake. Still, it can also occur in other situations that may cause thiamine deficiency, including bariatric surgery, gastrointestinal surgery, repeated vomiting, or hypermetabolic states[2]. Currently, there is no evidence to suggest a direct association between WE and non-alcoholic factors, such as nasopharyngeal carcinoma (NPC)[3]. NPC, which originates from the epithelial cells of the nasopharyngeal mucosa, exhibits a marked imbalance in its incidence across different geographical regions, being particularly prevalent in East and Southeast Asia[4]. This regional high-incidence phenomenon is closely associated with the geographic specificity of high-risk Epstein-Barr virus (EBV) subtypes[5,6]. Chemotherapy combined with radiotherapy is the primary treatment modality for locally advanced NPC[7]. Additionally, multiple studies have shown that induction chemotherapy combined with concurrent chemoradiotherapy can significantly improve the 10-year overall survival, progression-free survival, and reduce the rate of distant metastasis[8]. This report describes the diagnostic and therapeutic process, clinical manifestations, and imaging characteristics of a male patient with NPC who developed WE after concurrent chemoradiotherapy, with no history of alcohol abuse. We have followed the CARE guidelines[9] in reporting this case and obtained the patient's consent for treatment.

CASE PRESENTATION

Chief complaints

A young male patient with NPC, after undergoing four months of concurrent chemoradiotherapy, exhibited symptoms of altered mental status, impaired visual function, and gait ataxia (Figure 1).

History of present illness

On May 28, 2022, a 33-year-old young male sought treatment at Shaanxi Provincial People's Hospital for right ear fullness, right nasal congestion, and rhinorrhea with bloody discharge. After admission, a cranial magnetic resonance imaging (MRI) scan performed on May 31, 2022, indicated a mass on the right posterior superior wall of the nasopharynx, suggestive of a tumorous change, likely NPC, with bilateral cervical lymph node metastasis. A pathological examination confirmed the diagnosis of non-keratinizing undifferentiated NPC on the right side with bilateral cervical lymph node metastasis (T2N2M0 stage III). Immunohistochemical results were as follows: CK3(+), P63(+), KI-67 index approximately 80% (+), some residual FDC networks seen with CD21, partial positivity for CD56-CD20, positivity for CD interzone(+), and EGFR3(+). In situ hybridization showed EBV-encoded RNA epithelial cells (+). With reference to the guidelines[10], we performed image-guided intensity-modulated radiotherapy on this patient. The patient began definitive chemoradiotherapy for NPC on June 13, 2022, with doses of PGTVnx (GTVnx + external 3 mm): 7260 cGy/33 f, PGTVnd: 6600 cGy/33 f, PTV1: 6006 cGy/33 f, PTV2: 5445 cGy/33 f, all within the range for endangered organs. The last radiotherapy session was administered on August 7. Additionally, the patient started concurrent chemotherapy and targeted therapy on June 28, with doses of nimotuzumab 200 mg and cisplatin 80 mg/m^2 once a week for five weeks, with the last cycle on August 5. Apart from chemotherapy, treatments to prevent side effects of concurrent chemoradiotherapy included suppressing gastric acid secretion, antiemetics, maintaining electrolyte balance, and parenteral nutrition support (compound amino acid injection 18AA-VII, water-soluble vitamin injection, 20% fat emulsion injection C8-24Ve, potassium chloride

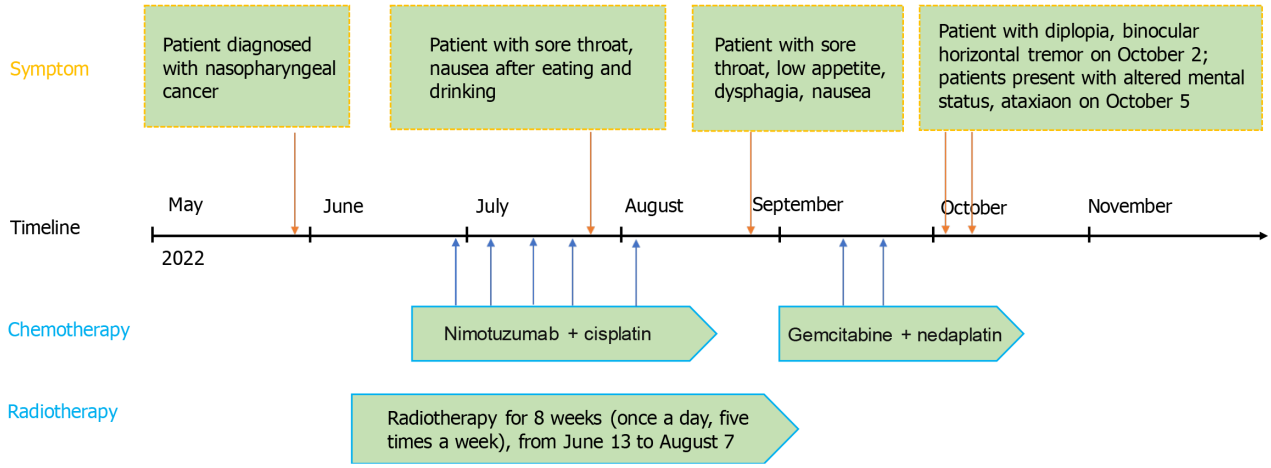

Figure 1 Timeline of the case.

injection, vitamin B6 injection, vitamin C injection). On July 23, the patient developed symptoms of sore throat and nausea after eating. Upon examination, his pharynx was found to be congested with scattered ulcers and hemorrhagic spots. Subsequently, he received symptomatic treatment with compound chlorhexidine gargle, topical recombinant human basic fibroblast growth factor, and traditional Chinese medicine preparations, but the symptoms did not completely resolve. On August 24, the patient again experienced a sore throat accompanied by itching and swallowing difficulties. Additionally, he frequently felt low appetite, nausea, and even vomiting. An electronic laryngoscopy confirmed the diagnosis of radiation laryngitis, an expected common side effect of head and neck radiotherapy. Clinicians treated him with Kangfuxin solution and changed the chemotherapy regimen on September 13 to gemcitabine 1600 mg/m^2 + nedaplatin 60 mg/m^2 based on his symptoms. There were two cycles of this chemotherapy phase, with the last on September 20. However, there was no significant relief. Starting September 29, the patient began to experience intermittent runny nose with yellow discharge, intermittent vomiting, and nausea. On the morning of October 2, the patient developed diplopia, horizontal nystagmus of both eyes, incomplete abducens nerve palsy of the right eye, and visual fatigue. He received treatment to alleviate visual fatigue. On October 5, the patient exhibited positional limb tremors, ataxic gait, unclear speech, and intermittent irritability.

History of past illness

The patient was in good health.

Personal and family history

Patient had no history of alcohol abuse, smoking, or allergies. His personal, marital, and family histories were unremarkable.

Physical examination

The patient's laboratory data were as follows: Temperature, 37.3 °C; pulse, 64 beats/minute (normal range: 60-100 beats/minute); blood pressure, 115/68 mmHg; respiratory rate, 21 breaths/minute; height, 184 cm; and weight, 63 kg [compared with the weight recorded on May 28 (96 kg), the patient's weight decreased by 33 kg]. The patient was alert and oriented [physical examination on admission (September 29)].

Laboratory examinations

Routine blood tests were immediately conducted, and the hematological parameters were as follows: White blood cell count, 5.73 × 10^9/L; neutrophil ratio, 0.891 (normal range: 0.4-0.75); lymphocyte ratio, 0.03 (normal range: 0.2-0.5); eosinophil ratio, 0.003 (normal range: 0.004-0.08); absolute lymphocyte count, 0.2 × 10^9/L [normal range: (1.1-3.2) × 10^9/L]; red blood cell count, 2.87 × 10^{12}/L (normal range: 4.35.8 × 10^{12}/L); hemoglobin, 90 g/L (normal range: 130-175 g/L); red cell distribution width, 0.15 (normal range: 0.116-0.146); hematocrit, 0.258 (normal range: 0.4-0.5); plateletcrit, 0.15 (normal range: 0.19-0.36). Serum liver function biochemical results were as follows: Cholinesterase, 3754 U/L (normal range: 5000-12000); total protein, 63.6 g/L (normal range: 65-85); albumin, 36.6 g/L (normal range: 40-55). Serum kidney function biochemical results were as follows: Potassium, 3.1 mmol/L (normal range: 3.5-5.5); sodium, 135 mmol/L (normal range: 137-147); chloride, 89 mmol/L (normal range: 96-108); magnesium, 0.62 mmol/L (normal range: 0.75-1.02); retinol-binding protein, 22.4 mg/L (normal range: 25-70 mg/L); cystatin-c, 1.050 mg/L (normal range: 0.59-1.030 mg/L). Serum thyroid function biochemical results were as follows: Free triiodothyronine, 2.5 pmol/L (normal range: 3.5-7.0 pmol/L); anti-thyroid peroxidase antibodies, 114.36 IU/mL (normal range: < 30 IU/mL). Serum anemia panel results were as follows: Vitamin B12, > 7344 pg/mL (normal range: 197-771 pg/mL); ferritin, 7760 ng/mL (normal range: 30-400 ng/mL) (laboratory tests on October 5).

Imaging examinations

Cranial MRI revealed symmetric patchy slightly prolonged T1 and T2 signal intensities bilaterally within the medial thalami, mammillary bodies, and surrounding the third and fourth ventricles, with slightly increased signal on FLAIR and DWI sequences, and ill-defined margins; the imaging diagnosis was symmetric patchy abnormal signal intensities around the third and fourth ventricles and in the medial thalami and mammillary bodies, consistent with WE (MRI on October 5) (Figure 2).

FINAL DIAGNOSIS

Final diagnosis is WE.

TREATMENT

After a neurology consultation, he was treated with thiamine injections 200 mg twice daily intramuscularly and enteral nutrition suspension 100 mL three times daily *via* nasogastric feeding. Considering the patient's medical history and imaging results, clinicians diagnosed WE, which was unrelated to his physical condition before admission but considered associated with thiamine deficiency during concurrent chemoradiotherapy. The diagnosis is based on four main aspects. Firstly, the observed reduction in dietary intake and nutritional imbalance following chemotherapy and radiotherapy were noted. Secondly, the patient exhibited three typical clinical manifestations of Wernicke encephalopathy: Ocular dysfunction, altered mental status, and gait ataxia. Additionally, the characteristic imaging features of Wernicke encephalopathy were confirmed through MRI examination. Lastly, significant alleviation of neurological symptoms was achieved after thiamine treatment. Before confirming the diagnosis, we excluded other potential diseases. Adverse reactions to radiotherapy and chemotherapy were the first factors we considered, such as common side effects in the treatment of NPC including thrombocytopenia, anemia, granulocytopenia, mucositis, dry mouth, dysphagia, loss of appetite, vomiting, nausea, weight loss, liver and kidney function damage, peripheral neuropathy, and temporal lobe damage[11]. Although these symptoms could explain some of the patient's clinical manifestations, they could not explain their MRI results. We also considered other diseases with similar MRI presentations as the patient, such as metronidazole encephalopathy and bilateral thalamic symmetric lesions (*e.g.*, top of the basilar syndrome, Creutzfeldt-Jakob disease, epidemic encephalitis B, *etc.*)[12], but the medical history and clinical features of these diseases did not match this case. Five days after starting thiamine treatment, the patient's mental state improved, which can be reflected by the accompanying symptoms of fatigue were significantly alleviated. After two weeks, the duration of symptoms such as diplopia and ocular tremor shows a declining trend. However, he continued to experience irritability and tremor after sitting up. Following the neurology consultation, he received an increased thiamine dosage, with injections of 300 mg twice daily and oral thiamine tablets of 100 mg three times daily. A week later, he transitioned to oral thiamine tablets 100 mg three times daily and was discharged.

OUTCOME AND FOLLOW-UP

At discharge, the patient's intermittent tremors had improved, but he still experienced horizontal diplopia, unstable knee and ankle reflexes in the left lower limb, a wide-based gait, and intermittent irritability. On February 9, 2023, a follow-up examination revealed that these symptoms persisted. A cranial MRI showed reduced lesions around the mammillary bodies and third ventricle, with previously observed "symmetrical patchy abnormal signal shadows around the medial thalami and fourth ventricle" now showing no significant abnormalities. In subsequent treatment, the patient adhered to a daily oral administration of thiamine three times (dosage of 10 mg), and regularly monitor the blood concentration of thiamine to ensure therapeutic efficacy.

DISCUSSION

WE is a neurological disorder caused by a deficiency in thiamine. Typically, thiamine must undergo several transport steps before it can function in brain cell metabolism. Thiamine ingested by the body is converted to its free form by intestinal phosphatases before entering enterocytes and then transferred across the intestinal epithelial cell membrane into the blood as thiamine pyrophosphate[13]. Thiamine in the blood exists in various forms, including free thiamine, three thiamine phosphates (monophosphate, diphosphate, and triphosphate), and adenosine thiamine triphosphate, among which thiamine diphosphate best reflects the body's thiamine reserve levels and is also the bioactive form of thiamine. Thiamine diphosphate is an essential coenzyme in several key biochemical pathways in the brain, primarily involved in aerobic glucose metabolism, the production and maintenance of myelin, and processes such as amino acid and glucose-derived neurotransmitters (such as glutamate, gamma-aminobutyric acid), *etc*[14]. A deficiency in thiamine leads to reduced metabolic activity of the tricarboxylic acid cycle and pentose phosphate pathway in specific neuronal and astroglial cells in the brain, subsequently causing intracellular lactate accumulation, decreased pH, and localized

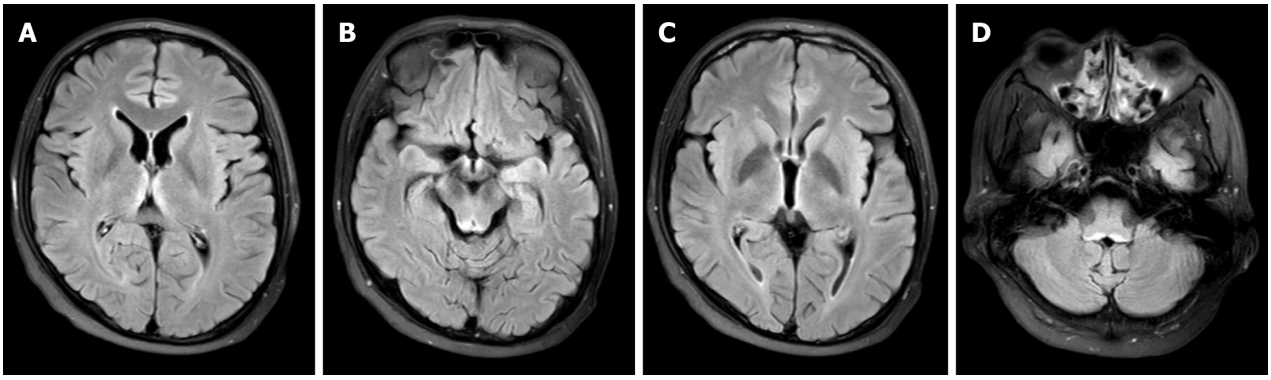

Figure 2 Magnetic resonance imaging of the brain. A: Bilateral symmetrical hyperintense signals on T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) around the medial thalamus; B: Bilateral symmetrical hyperintense signals on T2WI and FLAIR around the mammillary bodies; C: Bilateral symmetrical hyperintense signals on T2WI and FLAIR around the third ventricle; D: Bilateral symmetrical hyperintense signals on T2WI and FLAIR around the fourth ventricle.

acidosis in specific areas of the brain. These changes in cellular energy metabolism also cause mitochondrial dysfunction and intracellular oxidative stress, leading to astroglial cell dysfunction, such as promoting increased extracellular glutamate concentrations and disrupting the permeability of the blood-brain barrier[15]. The combined effect of these factors primarily causes disruption of the osmotic gradient across the cell membrane, cytotoxic edema, and these changes may be irreversible.

Computed tomography has limited value in identifying acute changes of Wernicke encephalopathy and is not the preferred imaging modality because, in most cases, it fails to identify the acute phase changes of Wernicke encephalopathy[16]. MRI of the brain can effectively display cytotoxic edema. Brain MRI shows that the medial thalami, perithird ventricular regions, periaqueductal areas, mammillary bodies, and the tectum of the midbrain are the areas most commonly affected by thiamine deficiency, manifesting as symmetrical T2-weighted and fluid-attenuated inversion recovery hyperintensities in the respective areas[17]. These regions are particularly sensitive to thiamine deficiency due to high rates of thiamine-related glucose and oxidative metabolism. Atypical MRI findings of Wernicke encephalopathy include symmetrical changes in the cerebellum, vermis, and cranial nerve nuclei[18], which are often associated with typical presentations. The European Federation of Neurological Societies guidelines indicate that MRI has a sensitivity of 53% and a specificity of 93% for diagnosing Wernicke encephalopathy[19]; therefore, a negative MRI does not rule out the diagnosis. In cases where clinical suspicion exists but MRI is negative, contrast-enhanced MRI can identify areas of blood-brain barrier disruption, reducing the incidence of false-negative MRI results[12]. However, imaging evidence alone cannot accurately identify Wernicke encephalopathy and must be combined with other aspects for a comprehensive diagnosis. Beyond imaging modalities, assessment of thiamine levels can also aid in diagnosis. Compared to direct measurement of free thiamine, its metabolite thiamine diphosphate more accurately reflects true thiamine levels. Additionally, analysis of erythrocyte transketolase activity by assessing changes in erythrocyte transketolase activity after adding exogenous thiamine pyrophosphate can diagnose thiamine deficiency. However, due to the lack of standardization of these assays[20], their practical application may be difficult to implement widely. Serum thiamine level testing is a common clinical method, but the concentration of thiamine in the blood does not necessarily reflect the concentration in brain tissue; thus, its value lies only in identifying suspected patients[21]. In terms of recognizing WE, medical and personal histories are important considerations that cannot be overlooked. The most common cause of thiamine deficiency is chronic alcoholism, but the possibility of Wernicke encephalopathy should also be considered in situations involving poor nutritional absorption and long-term parenteral nutrition support.

A multicenter observational study in Spain showed that non-alcoholic causative factors accounted for only 7% of the risk factors for Wernicke encephalopathy[22], which is similar to the analysis results of a nationwide retrospective cohort study in Switzerland[23]. Through the classification of risk factors in 4393 cases of Wernicke encephalopathy obtained from this study, we can find that patients with non-alcohol-related Wernicke encephalopathy account for 6.7% of all patients with Wernicke encephalopathy. Both studies suggest that the number of non-alcoholic Wernicke encephalopathy patients is small, but considering that the sample source of such studies is hospitalized patients with a clear diagnosis and the fact that Wernicke encephalopathy is currently underdiagnosed[1], these studies may overlook those unidentified non-alcoholic Wernicke encephalopathy patients. Therefore, the current clinical cases of non-alcoholic Wernicke encephalopathy are few, which is not a reason to neglect the disease. Existing research and case reports show that, in addition to alcoholism, a variety of factors can lead to Wernicke encephalopathy, including bariatric surgery, gastrointestinal surgery, hyperemesis gravidarum, malignant tumors, refeeding syndrome, dialysis status, thyrotoxicosis, inflammatory bowel disease, anorexia nervosa, sequelae of coronavirus disease 2019, *etc*[14,24-26]. Identifying these risk factors helps in screening for Wernicke encephalopathy. The screening and diagnosis of Wernicke encephalopathy are still primarily clinical diagnoses, and paying attention to the risk factors of the disease helps to keenly identify situations affecting thiamine intake. According to the guidelines of the European Federation of Neurological Societies[19], after considering the characteristic of reduced thiamine absorption, patients only need to meet two of the typical triad of features of Wernicke encephalopathy to be clinically diagnosed with Wernicke encephalopathy, which undoubtedly reduces the false-negative results of clinical diagnosis.

In a systematic review of 586 cases of non-alcoholic Wernicke encephalopathy[27], researchers found that the causative factors of non-alcoholic Wernicke encephalopathy attributed to malignant tumors accounted for 22%, and among these, 76% of patients had hematologic or gastrointestinal malignancies. A similar view can be drawn from another systematic review[28], which is that Wernicke encephalopathy caused by malignant tumors occupies a smaller proportion in the studied population, with NPC being even less common. Considering the current lack of epidemiological studies on Wernicke encephalopathy, although these two studies have publication bias and detection bias, they indicate that we must pay attention to the possibility of Wernicke encephalopathy occurring in cancer populations.

Currently, there is a paucity of research on the phenomenon of Wernicke encephalopathy in patients with malignant tumors. Existing studies suggest that the high metabolic characteristics of malignant tumors may promote the consumption of thiamine, which could be the cause of thiamine deficiency, commonly seen in hematologic malignancies[28]. Past case reports indicate that surgery or reduced intake in patients with gastrointestinal malignancies are potential factors precipitating Wernicke encephalopathy[29-31]. However, for NPC, there are currently no distinct features suggesting a potential correlation with the occurrence of Wernicke encephalopathy. In a randomized controlled trial using fedratinib to treat myelofibrosis, researchers found that four patients receiving fedratinib developed Wernicke encephalopathy[32] and another patient with lung cancer undergoing treatment with nivolumab developed Wernicke encephalopathy during therapy[33]. This could potentially suggest that certain therapeutic agents for malignant tumors might be potential precipitating factors for Wernicke encephalopathy; however, more cases are needed to support this view.

Early diagnosis of Wernicke encephalopathy and prompt administration of thiamine are crucial to preventing the progression to Korsakoff syndrome. Korsakoff syndrome, characterized by severe anterograde and retrograde amnesia, is caused by unrecognized or insufficiently treated Wernicke encephalopathy[34], and currently, there is no fully validated pharmacological treatment[35]. Compared to Wernicke encephalopathy, the chronic phase, namely Korsakoff syndrome, clinically presents with abnormal mental states, and disproportionate impairment of episodic memory function relative to other cognitive functions affected[36]. Neuropathological studies suggest that damage to the anterior nuclei of the thalamus also differs from the pathological changes in Wernicke encephalopathy; a study by NSWTRC demonstrates that damage to the tissue of the anterior nuclei of the thalamus is a key lesion leading to the severe memory impairment in Korsakoff syndrome[37]. Research on the progression from Wernicke encephalopathy to Korsakoff syndrome remains insufficient, but inadequate treatment is a plausible explanation for disease progression.

In animal experiments, there are conflicting views on the effect of additional thiamine supplementation on malignant tumors. Some studies indicate that extra thiamine increases the incidence of bladder cancer in rats and can inhibit the cytotoxicity of methotrexate; on the other hand, MDA231 breast cancer xenografts show delayed proliferation in mice on a thiamine-free diet[38]. Such studies demonstrate the dual characteristics of thiamine in both inhibiting and promoting cancer development, which may be related to different types of cancer or genetic factors, and more research is needed to support these viewpoints. However, preventive interventions for populations at risk of Wernicke encephalopathy have gained more recognition. Some scholars, considering the high risk of thiamine deficiency after bariatric surgery, suggest early screening and postoperative supplementation to prevent Wernicke encephalopathy[39]. Similarly, the European Federation of Neurological Societies guidelines recommend parenteral thiamine supplementation after bariatric surgery [19]. Nevertheless, a real-world study exploring the appropriate dosage of preventive thiamine supplementation in populations at risk of Wernicke encephalopathy found no significant difference in any cognitive outcome measures across different doses[40]. This suggests that we need to uncover more evidence to verify the reliability of preventive interventions.

CONCLUSION

In summary, during the treatment of malignant tumors, oncologists should provide nutritional support throughout the process and be aware of the possibility of this disease's occurrence, and timely detection and early intervention are necessary.

FOOTNOTES

Author contributions: Ma YY and He XC contributed equally to this work and should be considered co-first authors. Ma YY acquired and analysed the work, drafted the manuscript, and collected and analysed the images; He XC, Gao Y, and Ma TT edited the manuscript; Cheng G and Yue CW wrote, proofread, and edited the manuscript, they contributed equally to this work and should be considered co-corresponding author; all authors have met the authorship requirements for the submitted version and have agreed to its submission.

Informed consent statement: The patient consented to treatment and provided written consent for publication of this study. we have de-identified the information regarding the patients that is included in the article.

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