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Contents

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EDITORIAL

Fan YH, Wang MW, Gao YN, Li WM, Jiao Y. Genetic and environmental factors influencing Crohn's disease. *World J Gastrointest Surg* 2025; 17(3): 98526 [DOI: 10.4240/wjgs.v17.i3.98526]

Pandey CK, Kumar A. Perioperative neurocognitive dysfunction and role of dexmedetomidine in radical colon cancer surgery in elderly patients. *World J Gastrointest Surg* 2025; 17(3): 100126 [DOI: 10.4240/wjgs.v17.i3.100126]

Wang Y, Xun X, Luan WY, Zhang Z, Xu ZX, Lin SX, Miao YD. Hyperthermia combined with opioid therapy: Enhancing cancer pain management and reducing surgical stress in gastrointestinal cancer patients. *World J Gastrointest Surg* 2025; 17(3): 101060 [DOI: 10.4240/wjgs.v17.i3.101060]

Li LQ, Jiao Y. Risk and management of adverse events in minimally invasive esophagectomy. *World J Gastrointest Surg* 2025; 17(3): 103941 [DOI: 10.4240/wjgs.v17.i3.103941]

MINIREVIEWS

Deng SS, Zhu YP, Chen ZT, Li W. Application progress of early nutrition intervention in patients with hepatocellular carcinoma after liver transplantation. *World J Gastrointest Surg* 2025; 17(3): 100321 [DOI: 10.4240/wjgs.v17.i3.100321]

Feng LF, Li XW, Zhu XQ, Jin LN. Advances in management strategies for enteral nutrition-related gastric retention in adult patients with nasogastric tubes. *World J Gastrointest Surg* 2025; 17(3): 101751 [DOI: 10.4240/wjgs.v17.i3.101751]

Wu L, Wu H, Mu S, Li XY, Zhen YH, Li HY. Surgical approaches for complete rectal prolapse. *World J Gastrointest Surg* 2025; 17(3): 102043 [DOI: 10.4240/wjgs.v17.i3.102043]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Liu M, Feng B, He N, Yan R, Qin J. Efficacy of fluorouracil combined with paclitaxel and oxaliplatin for the treatment of advanced gastric signet ring cell carcinoma. *World J Gastrointest Surg* 2025; 17(3): 94286 [DOI: 10.4240/wjgs.v17.i3.94286]

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Zhao L, Wei L, Fei XL. Impact of diabetes on recovery after radical gastrectomy for gastric cancer: A retrospective cohort study. *World J Gastrointest Surg* 2025; 17(3): 100763 [DOI: 10.4240/wjgs.v17.i3.100763]

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Retrospective Study

Yu Y, Wang XQ, Liu G, Li L, Chen LN, Zhang LJ, Xia Q. Impact of a visual mobile terminal-based continuity of care model on caregiver competence of children with enterostomies. *World J Gastrointest Surg* 2025; 17(3): 99099 [DOI: 10.4240/wjgs.v17.i3.99099]

Chen DX, Fang KX, Chen SX, Hou SL, Wen GH, Yang HK, Shi DP, Lu QX, Zhai YQ, Li MY. Optimal timing of endoscopic biliary drainage for bile duct leaks: A multicenter, retrospective, clinical study. *World J Gastrointest Surg* 2025; 17(3): 99425 [DOI: 10.4240/wjgs.v17.i3.99425]

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Lou QX, Xu KP. Analgesic effect and safety of dexmedetomidine-assisted intravenous-inhalation combined general anesthesia in laparoscopic minimally invasive inguinal hernia surgery. *World J Gastrointest Surg* 2025; 17(3): 99597 [DOI: 10.4240/wjgs.v17.i3.99597]

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Li J, Chen JP, Lai CH, Fu L, Ji Y. Efficacy of water infusion combined with defoamers in colonoscopy. *World J Gastrointest Surg* 2025; 17(3): 99784 [DOI: 10.4240/wjgs.v17.i3.99784]

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Li M, Yuan DH, Yang Z, Lu TX, Zhang L. Retrospective analysis of preoperative tumor marker levels in rectal cancer patients: Implications for diagnosis. *World J Gastrointest Surg* 2025; 17(3): 100820 [DOI: 10.4240/wjgs.v17.i3.100820]

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Eray IC, Topal U, Gumus S, Isiker K, Yavuz B, Aydin I. Comparative analysis of Ferguson hemorrhoidectomy combined with doppler-guided hemorrhoidal artery ligation and Ferguson hemorrhoidectomy in hemorrhoidal disease treatment. *World J Gastrointest Surg* 2025; 17(3): 103953 [DOI: 10.4240/wjgs.v17.i3.103953]

Clinical Trials Study

Zhu LL, Shen RZ. Follow-up of elderly gastric cancer post-radical surgery: Trauma, complications, and prognosis. *World J Gastrointest Surg* 2025; 17(3): 100143 [DOI: 10.4240/wjgs.v17.i3.100143]

Observational Study

Hu G, Ma J, Qiu WL, Mei SW, Zhuang M, Xue J, Liu JG, Tang JQ. Patient selection and operative strategies for laparoscopic intersphincteric resection without diverting stoma. *World J Gastrointest Surg* 2025; 17(3): 95983 [DOI: 10.4240/wjgs.v17.i3.95983]

Randomized Controlled Trial

Tan XQ, Huang XL. Effects of postoperative quantitative assessment strategy-based nursing in patients with colorectal cancer. *World J Gastrointest Surg* 2025; 17(3): 100302 [DOI: 10.4240/wjgs.v17.i3.100302]

SYSTEMATIC REVIEWS

Isah AD, Wang X, Shaibu Z, Yuan X, Dang SC. Systematic review and meta-analysis comparing extraperitoneal and transperitoneal routes of colostomy-related complications. *World J Gastrointest Surg* 2025; 17(3): 98947 [DOI: 10.4240/wjgs.v17.i3.98947]

SCIENTOMETRICS

Wang XY, Chen HY, Sun Q, Li MH, Xu MN, Sun T, Huang ZH, Zhao DL, Li BR, Ning SB, Fan CX. Global trends and research hotspots in esophageal strictures: A bibliometric study. *World J Gastrointest Surg* 2025; 17(3): 100920 [DOI: 10.4240/wjgs.v17.i3.100920]

CASE REPORT

Chen JT, Li YP, Guo SQ, Huang JS, Wang YG. Nonsurgical treatment of postoperative intestinal obstruction caused by heterotopic ossification of the mesentery: A case report. *World J Gastrointest Surg* 2025; 17(3): 99015 [DOI: 10.4240/wjgs.v17.i3.99015]

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Tian ZS, Ma XP, Ruan HX, Yang Y, Zhao YL. Rare large sigmoid hamartomatous polyp in an elderly patient with atypical Peutz-Jeghers syndrome: A case report. *World J Gastrointest Surg* 2025; 17(3): 102174 [DOI: 10.4240/wjgs.v17.i3.102174]

LETTER TO THE EDITOR

Deng HZ, Liu YF, Zhang HW. Role of two-dimensional shear wave elastography in predicting post-hepatectomy liver failure: A step forwards in hepatic surgery. *World J Gastrointest Surg* 2025; 17(3): 98454 [DOI: 10.4240/wjgs.v17.i3.98454]

Rao AG, Nashwan AJ. Enhancing endoscopic retrograde cholangiopancreatography safety: Predictive insights into gastric retention. *World J Gastrointest Surg* 2025; 17(3): 98898 [DOI: 10.4240/wjgs.v17.i3.98898]

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Pavlidis ET, Galanis IN, Pavlidis TE. Current opinions on the use of prophylactic antibiotics in patients undergoing laparoscopic cholecystectomy. *World J Gastrointest Surg* 2025; 17(3): 101938 [DOI: 10.4240/wjgs.v17.i3.101938]

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Contents

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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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EDITORIAL

Genetic and environmental factors influencing Crohn's disease

Ye-Hui Fan, Ming-Wei Wang, Yu-Ning Gao, Wen-Mao Li, Yan Jiao

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Abstract

This editorial discusses Pellegrino and Gravina's essay. Crohn's disease (CD) is a complex and multifactorial disease that is influenced by a combination of genetic and environmental factors. While genetic factors play a key role in the development of the disease, environmental factors also play a significant role in influencing the risk of developing CD. By looking at present understanding of CD pathogenesis, we emphasize the important factors involved in the development of this illness, such as nucleotide-binding oligomerization domain-2, smoking, and vitamin D. Understanding the interplay between genetic and environmental factors is crucial for developing effective strategies for preventing and treating this chronic inflammatory bowel disease.

Key Words: Crohn's disease; Pathogenesis; Nucleotide-binding oligomerization domain-2; Smoking; Vitamin D

Core Tip: The link and complicated mechanisms between Crohn's disease (CD), nucleotide-binding oligomerization domain-2, smoking, and vitamin D is complex and poorly understood. In addition to genetic and environmental factors, the interaction between the two is also thought to play a role in the development of CD. Furthermore, the consequences of CD differ from person to person, emphasizing the importance of individual therapy. Individualized treatment, including surgery and medications, is important.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that affects millions of individuals worldwide[1]. This debilitating condition is characterized by inflammation of the lining of the digestive tract, leading to a range of symptoms including abdominal pain, diarrhea, weight loss, and fatigue[2]. The exact cause of CD remains unknown, but it is believed to result from a complex interplay of genetic, environmental, and immune factors[3]. About 60%-70% of CD patients may experience complications such as abdominal abscess, intestinal obstruction, intestinal perforation, intestinal fistula, intestinal leakage, and gastrointestinal bleeding in the later stage, requiring one or even multiple surgical treatments[4]. A key feature of CD is dysregulation of the immune response, with an exaggerated inflammatory response to intestinal bacteria believed to play a central role in the development of the disease[5]. Genetic factors also contribute to the risk of developing CD, with certain genetic variations known to increase susceptibility to this condition[6]. Environmental factors such as diet, smoking, and the composition of the gut microbiota are also thought to play a role in triggering or exacerbating inflammation in individuals predisposed to CD[7]. The colonic bacterial composition in CD is altered compared to healthy individuals, and this dysbiosis, an imbalance in the microbial community, appears to contribute to both the onset and the exacerbation of inflammation in the gut. Table 1 summarized the potential factors influencing CD.

GENETIC FACTORS

Genetic factors have long been recognized as playing a key role in the development of CD. In fact, having a first-degree relative with CD can increase the risk of developing the disease by up to 20 times. Variants in the nucleotide-binding oligomerization domain-2 (*NOD2*) gene, involved in the immune response to bacteria in the gut, could increase risk of developing CD.

NOD2 mutations are associated with some phenotypes of CD, such as fibrous stenosis or penetrating lesions[8]. *NOD2* gene deficiency leads to intestinal inflammatory gene expression and dysfunction of goblet cells in the intestinal mucosa in mice. These abnormalities are related to excessive production of kinesin by intestinal mucosal intraepithelial lymphocytes. In addition, scholars also detected an increase in the number of pro-inflammatory microorganisms Bacteroides in the gut. The mice with *NOD2* mutation have autophagy dysfunction and increased bacterial lipopolysaccharide, which leads to the activation of Toll like receptors, the massive release of a variety of inflammatory related factors and the waterfall like effect, and finally causes intestinal inflammatory response[9].

The identification of these genetic risk factors has helped to improve our understanding of the underlying mechanisms that drive the development of CD. For example, studies have shown that mutations in the *NOD2* gene can lead to an abnormal immune response in the gut, leading to inflammation and damage to the intestinal lining. Other genetic variants have been linked to abnormalities in the gut microbiome, the community of bacteria that live in the intestines and play a crucial role in regulating the immune system.

GENETIC VARIANTS TO IMPROVE THE EFFECTIVENESS OF DIAGNOSIS AND TREATMENT

Over the last few decades, CD-associated genetic variants largely affect immune responses, intestinal barrier function, and microbial interactions. Variants in the IL23R gene, which play a crucial role in the regulation of T-cell responses, are also strongly associated with CD. The involvement of IL23R in immune cell regulation suggests a potential therapeutic target. ATG16 L1 and IRGM are involved in autophagy, a process critical for the immune response to pathogens. Mutations in these genes can lead to impaired autophagy and contribute to CD pathogenesis. Variants in TNF Superfamily Member 15 have been linked to an increased risk of CD, particularly in European and Asian populations, suggesting a role in the regulation of inflammation. While genetic testing for CD is not yet routine in clinical practice, it holds potential in early diagnosis. Identifying patients at high genetic risk could enable earlier intervention, potentially altering the disease course. Moreover, genetic variants such as those affecting drug metabolism can influence a patient's

Table 1 The potential factors influencing Crohn's disease

Pathogenesis	Factors	Description
Genetic factors	*NOD2*	*NOD2* is involved in recognizing bacterial components and activating innate immune responses. Mutations in *NOD2* are one of the most well-established genetic risk factors for CD, particularly influencing the response to intestinal bacteria
	ATG16 L1	ATG16 L1 is critical for autophagy, the process by which cells degrade and recycle components. Variants in this gene impair autophagy, which can increase susceptibility to CD by disrupting immune tolerance and promoting chronic inflammation
	TLRs	TLRs are part of the innate immune system, helping to recognize pathogens and initiate immune responses. Dysregulated TLR signaling can lead to an exaggerated immune response to gut microbiota, contributing to CD
Environmental factors	Smoking	Smoking is a well-established environmental risk factor for CD. It alters immune responses and microbiome composition, and is associated with more severe disease progression and complications, such as strictures and fistulas
	Diet	A diet high in processed foods, fats, and sugar, and low in fiber, can promote gut inflammation and dysbiosis, which may trigger or exacerbate CD. Diets rich in omega-3 fatty acids and fiber may have protective effects
	Vitamin D	Low levels of vitamin D have been associated with an increased risk of developing CD and may affect immune function. Vitamin D plays a role in regulating the immune system and maintaining the intestinal barrier
Gut microbiota	Bacteria	Dysbiosis, or an imbalance in gut bacterial composition, is linked to CD. Pathogenic bacteria like Escherichia coli may promote inflammation, while beneficial bacteria like *Faecalibacterium prausnitzii* have anti-inflammatory effects
	Fungi	The gut mycobiome (fungal microbiota) has been found to differ in CD patients compared to healthy controls. Dysregulated fungal populations may interact with bacteria, affecting immune responses and intestinal barrier function
	Virus	Viral infections, particularly those that affect the gut, may trigger or exacerbate CD in genetically susceptible individuals. Viruses like enteric adenoviruses and Epstein-Barr virus have been implicated in IBD pathogenesis
	Parasite	Parasitic infections may modulate immune responses, potentially either triggering or protecting against inflammation. Some studies suggest that exposure to certain parasites may be protective against CD
Immune factors	Innate immunity	Innate immunity involves the body's first line of defense, including pattern recognition receptors. Dysregulation in innate immunity leads to an inappropriate immune response to normal gut bacteria, contributing to chronic inflammation in CD
	Acquired immunity	The acquired immune response involves T cells and antibodies. In CD, an imbalance of Th1 and Th17 responses can drive inflammation, while Tregs may be insufficient to control it. Abnormal cytokine production is a key feature of CD
Non-coding RNA	miRNA	miRNAs are small RNA molecules that regulate gene expression post-transcriptionally. In CD, altered miRNA expression can affect immune cell differentiation and response, potentially contributing to inflammation and disease progression
	lncRNA	lncRNAs are involved in the regulation of gene expression, chromatin remodeling, and immune cell differentiation. Their dysregulation in CD may impact immune function and contribute to intestinal inflammation
	siRNA	siRNAs regulate gene silencing and play a role in modulating immune responses. They have been explored as potential therapeutic agents for targeting specific genes involved in CD pathogenesis
	circRNA	circRNAs are a type of non-coding RNA that form closed loops. They are involved in regulating gene expression and protein activity. In CD, altered circRNA expression may influence immune responses and gut barrier integrity

NOD2: Nucleotide-binding oligomerization domain-2; ATG16 L1: Autophagy related 16 like 1; TLRs: Toll-like receptors; CD: Crohn's disease; Tregs: Regulatory T cells; IBD: Inflammatory bowel disease.

response to medications and their risk of adverse effects.

ENVIRONMENT FACTORS

Several environmental risk factors have been identified, including smoking, diet, and stress. Smoking is one of the most well-established environmental risk factors for CD, with smokers being twice as likely to develop the disease compared to non-smokers. Studies have shown that smoking can disrupt the balance of bacteria in the gut and increase inflammation, contributing to the development of CD.

Smoking as one environmental factor has long been recognized as a risk factor for several health conditions, including heart disease, lung cancer, and respiratory problems. Recently, smoking has been of particular interest in relation to CD. Several studies have suggested that smoking may have a significant impact on the development and progression of CD [10,11]. For instance, research has shown that smoking can increase the risk of developing CD in individuals with a genetic predisposition to the condition[12]. Additionally, smokers with CD may experience more severe symptoms, require more aggressive treatment, and have a higher risk of complications compared to non-smokers with the condition. Chronic smokers, particularly those who have smoked for many years, are at an increased risk of developing CD, with

studies indicating that smoking may accelerate disease onset and increase the severity of symptoms. Smoking duration and intensity are important factors in modulating disease outcomes, with heavy smokers experiencing more frequent flare-ups and complications compared to non-smokers. Both active smoking and passive exposure to tobacco smoke have been associated with increased disease risk. However, the risk is significantly higher in active smokers. While the exact mechanisms remain unclear, smoking-induced changes in the gut's immune system and microbiota are believed to play a key role in the pathogenesis of CD.

Diet is another important environmental factor that can influence the development of CD. Research has shown that a diet high in processed foods, sugar, and saturated fats can increase inflammation in the gut and disrupt the balance of bacteria, contributing to the development of the disease. In contrast, a diet high in fruits, vegetables, and fiber has been shown to reduce inflammation and promote a healthy gut microbiome, reducing the risk of developing CD.

Vitamin D plays an important role in the pathogenesis by participating in the regulation of intestinal immune function [13]. Most patients with CD are complicated with vitamin D deficiency, and the reduction of vitamin D is significantly correlated with the incidence of CD[14]. The 1,25-dihydroxyvitamin D3 can significantly increase the secretion of antimicrobial peptides by Paneth cells in the intestinal mucosa through binding with vitamin D receptor, and promote the development and differentiation of regulatory T cells and type 2 helper T cells[15]. Vitamin D also affects the function of natural killer T cells and reduces the production of related cytokines such as Thl7 cells. In addition, vitamin D can protect patients with CD by increasing the number and abundance of beneficial bacteria and regulating the polymorphism of bacteria in the gut[16]. And vitamin D supplementation can reduce the recurrence rate of CD. The threshold for vitamin D deficiency commonly used in clinical practice is typically below 20 ng/mL (50 nmol/L), which is consistent with the definition of deficiency from organizations like the Institute of Medicine and the Endocrine Society. Levels between 20-30 ng/mL are considered insufficient, while levels above 30 ng/mL are generally considered sufficient for bone and immune health. Most studies implicating vitamin D in CD have linked deficiency levels (under 20 ng/mL) with poorer disease outcomes, such as higher disease activity, increased flare-ups, and poorer response to treatment. Vitamin D deficiency may be associated with the development of CD[17].

There are also some other environmental factors such as smoking e-cigarettes, exposure to various food toxicants, *etc.* The use of e-cigarettes is increasingly common, and while it is considered less harmful than traditional smoking, emerging evidence suggests it may still have a detrimental effect on gut health. E-cigarette vapors contain various chemicals, such as nicotine, formaldehyde, and acrolein, which can alter the gut microbiota, increase oxidative stress, and trigger inflammatory responses. Nicotine, in particular, may exacerbate CD by promoting Th17-mediated inflammation and impairing mucosal immunity. The long-term effects of vaping on CD are not fully understood but may include the potential to exacerbate existing disease or trigger the onset in susceptible individuals. Exposure to environmental pollutants, including particulate matter (PM2.5), NO_2, and O_3, has been associated with an increased risk of inflammatory bowel diseases, including CD. These pollutants can promote systemic inflammation, affect the gut immune response, and disrupt the microbiome.

EFFECT OF UNHEALTHY DIET, AND LIFESTYLE

Diets high in sugar, processed foods, and refined carbohydrates (*e.g.*, white bread, sugary drinks, and sweets) have been shown to promote inflammation in the body. These foods can trigger or worsen flare-ups of CD by aggravating the gut's immune response. Diets rich in unhealthy fats, particularly trans fats and saturated fats, have been linked to increased intestinal inflammation. Excess fat intake can promote the production of pro-inflammatory cytokines, which increase gut inflammation and can contribute to the severity of Crohn's symptoms.

CLINICAL IMPLICATIONS

Despite these findings, the link between CD, *NOD2*, smoking, and vitamin D is complex and poorly understood. In addition to genetic and environmental factors, the interaction between the two is also thought to play a role in the development of CD. Similarly, environmental factors may influence the expression of certain genes that increase the risk of developing the disease. Furthermore, the consequences of CD differ from person to person, emphasizing the importance of individual therapy. The complicated mechanisms underlying the link between CD, *NOD2*, smoking, and vitamin D need to be studied further for therapeutic applications. Individualized management, including surgery and medicines, is significant[18].

CONCLUSION

While genetic factors play a key role in the development of the disease, environmental factors also play a significant role in influencing the risk of developing CD. By looking at present understanding of CD pathogenesis, we emphasize the important factors involved in the development of this illness, such as *NOD2*, smoking, and vitamin D. Understanding the interplay between genetic and environmental factors is crucial for preventing and treating this chronic inflammatory bowel disease.

FOOTNOTES

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EDITORIAL

Perioperative neurocognitive dysfunction and role of dexmedetomidine in radical colon cancer surgery in elderly patients

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Abstract

This article explored the application of dexmedetomidine (Dex), a highly selective alpha-2 agonist, in managing postoperative cognitive dysfunction (POCD) in elderly patients undergoing radical colon cancer surgery. Aging is associated with a progressive decline in physiological functions and an increased risk of adverse surgical outcomes, including POCD, which encompasses many neurocognitive disorders that manifest during the perioperative period. The aging population is at a higher risk for POCD, which can lead to prolonged hospital stays, delayed recovery, and increased healthcare costs. Dex has neuroprotective, opioid-sparing, and sympatholytic properties, which reduces the incidence and severity of POCD. Dex was introduced for sedation in patients receiving mechanical ventilation but has since been adopted in anesthesia due to its multifaceted benefits. Its application extends to sedation, analgesia, maintenance of anesthesia, and controlling delirium. Its neuroprotective and anti-inflammatory effects have been explored in managing POCD. This article discussed the broad range of patient and procedure-related risk factors for POCD. Early identification and intervention are crucial to prevent the progression of POCD, which can have severe physical, psychological, and economic consequences. The article underscored the importance of a multidisciplinary approach in managing POCD, involving the optimization of comorbidities, depth of anesthesia monitoring, hemodynamic stability, and cerebral oxygenation monitoring.

Key Words: Colon cancer; Dexmedetomidine; General anesthesia; Elderly; Radical colon cancer surgery; Cognitive function

Core Tip: Dexmedetomidine (Dex) is a significant drug that improves surgical outcomes in varied surgeries. The neuroprotective, opioid-sparing, and sympatholytic properties of Dex have shown improved outcomes in the elderly population in various surgeries including radical colon surgeries. The decline in the incidence and severity of postoperative cognitive dysfunction, the decreased surge in proinflammatory markers, improved regional cerebral oxygenation, and better pain control due to Dex lead to improved outcomes, early discharge, and decreased healthcare costs in this vulnerable group of patients.

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INTRODUCTION

Aging is associated with a progressive decline in the physiological function of all organ systems along with other major comorbidities and increased vulnerability to anesthesia drugs[1,2]. Frailty in the older population is associated with aging-related functional capacity decline and reduced tolerance to surgical interventions[3]. However, there is variability in the onset and severity of these physiological derangements. Major surgeries in this vulnerable population group carry a significant risk of adverse outcomes[4]. The major adverse outcomes include major adverse cardiac events[5], pulmonary complications[6], renal impairments[7], and postoperative cognitive dysfunction (POCD). Among the adverse outcomes associated with major surgeries in this population, perioperative neurocognitive disorder (PND) stands out due to its high prevalence and significant impact. POCD is associated with poor wound healing, delayed mobilization, prolonged hospital stays, hospital readmission[8], and delay in resumption of routine lifestyle[9].

The incidence of colon cancer has increased in the elderly population in the past few decades due to altered lifestyles, prolonged life expectancy, better screening, and increased awareness[10]. With the advancement in surgical and anesthesia techniques, a large number of the elderly population is subjected to surgical interventions. Radical colon surgeries are curative surgeries that include the removal of colon segments and lymph nodes. Enhanced recovery protocols after colorectal surgeries are aimed at early hospital discharge while minimizing perioperative physiological disturbances[11].

PND is a broad term that includes abnormalities in behavior, affect, and cognition in the perioperative period and is included in the Diagnostic and Statistical Manual 5th edition terminology for neurocognitive disorder. PND is a well-recognized adverse complication in the elderly population that causes delays in the recovery of patients and prolongs hospital stays. PND includes entities like preexisting cognitive impairment, postoperative persistent or recurrent delirium, delayed neurocognitive recovery, and major or minor neurocognitive decline that persists or is diagnosed up to 12 months after the procedure[12]. The exact mechanism of PND is unclear, but risk factors are broadly classified into patient and procedure-related. The patient-related factors include age > 65 years, dementia, neurodegenerative disorder, excessive alcohol consumption, polypharmacy including psychotropic drugs, vascular disorders, sleep disorders, diabetes mellitus, and prior neuron damage like stroke or traumatic brain injury and frailty[13-15]. The procedure-related factors include major complex surgeries like open cardiac surgeries and joint arthroplasties, head and neck surgeries, and colorectal surgeries[16-19]. The incidence of postoperative delirium in colorectal surgeries ranges from 8% to 54%[20].

The exact pathophysiological mechanisms of PND are unclear, but systemic inflammatory responses to perioperative stress causing excessive neuroinflammation and exaggerated neurodegeneration have been postulated as the main cause of PND[21,22]. Patient and procedure-related factors mentioned above can change the extent and severity of these inflammatory processes. Dexmedetomidine (Dex) is a highly selective alpha-2 agonist that acts *via* activation of G protein-coupled receptors in the brainstem inhibiting norepinephrine release[23]. Dex was initially introduced in 1999 for sedation in patients receiving mechanical ventilation. Thereafter, the use of Dex has exploded in anesthesia as an "all-in-one drug." The pharmacological properties of Dex have been widely explored, and it has been used in sedation, analgesia, sympatholysis, maintenance of anesthesia, delirium control, awake intubation, and procedural sedation[24]. Interestingly, the neuroprotection and anti-inflammatory properties of the drug were further explored to control PND. The systematic reviews and meta-analyses published in recent years have established the beneficial role of Dex in preventive cognitive dysfunction in cardiac[25,26] and noncardiac surgeries[27,28]. Bu *et al*[29] in their randomized control trial (RCT) have also concluded that Dex decreases cognitive dysfunction in radical colon cancer surgeries in the elderly. The article gives an insight into perioperative cognitive dysfunction and pharmacological intervention by Dex to prevent PND.

NEUROCOGNITIVE DYSFUNCTION

PND is a broader term used for various clinical entities involving behavior, affect, and cognition in the perioperative period[12]: (1) Preexisting cognitive impairment (diagnosed in the preoperative period); (2) Postoperative persistent or recurrent delirium (beyond the emergence period of general anesthesia); (3) Delayed neurocognitive recovery (diagnosed

30 days after surgery); and (4) Major or minor neurocognitive decline (diagnosed after 12 months after surgery). POCD is a generalized term often used to diagnose any postoperative cognitive impairment and is often used in clinical studies. POCD is a clinical diagnosis, and the Montreal Cognitive Assessment/Mini-Mental State Examination (MMSE) scales are often used to diagnose and assess the severity of impairment[30] (the same scale was used in the RCT by Bu *et al*[29]). A preoperative cognitive screening should be performed using MMSE or a shorter scale such as Mini-Cog as a baseline measurement[31-33]. Similarly, postoperative evaluation should be performed using the same scale to detect any decline in cognition. A patient with risk factors of PND should undergo regular screening at timely intervals for early detection, while all the preventive measures are carried out simultaneously.

PND is associated with delayed recovery, increased hospitalization period, increased mortality, and increased medical costs. There can be impairment of mood, memory, emotions, behavior, sleep, and personality. Even a short period of postoperative cognitive impairment can lead to permanent cognitive dysfunction like Alzheimer's disease and dementia causing severe physical and psychological impact and loss of independence[34-36]. Thus, it is imperative to identify risk factors to prevent PND, and early clinical recognition is important to prevent progressive deterioration.

SYSTEMIC INFLAMMATION AND NEUROPROTECTION

The exact mechanisms responsible for neurocognitive disorder are still not clear. Inflammatory processes due to perioperative stress cause neuronal damage and neuroinflammation[20]. Microemboli causing neuronal injury due to blood clots or air have also been proposed as possible mechanisms. Inflammatory biomarkers play a critical role in the development of PND through their contributions to systemic and central inflammatory responses. Tumor necrosis factor-alpha promotes microglial activation and blood-brain barrier disruption, leading to increased permeability and neuronal injury. Interleukin (IL)-1β amplifies this process by further activating microglia and inducing neuroinflammation, which exacerbates cognitive decline. IL-6, another key cytokine, is involved in the acute-phase response and has been correlated with both the severity and duration of PND.

The calcium-binding protein S100B is a marker of blood-brain barrier disruption and direct neuronal injury. Elevated levels of S100B indicate neuroinflammation and correlate with cognitive dysfunction. Similarly, C-reactive protein, a systemic inflammatory marker, reflects the presence of nonspecific acute-phase responses and has been associated with prolonged POCD. Neuron-specific enolase (NSE), a biomarker of neuronal damage, further underscores the link between inflammation and cognitive impairment. Targeting inflammatory pathways, such as toll-like receptor signaling and nuclear factor kappa B activation, offers a therapeutic avenue[37]. Dex, through its anti-inflammatory effects, could potentially modulate these responses, attenuating neuroinflammation and preserving cognitive function in the perioperative period. Clinical studies have measured these inflammatory markers to establish an association with PND.

Elevated serum levels of systemic inflammatory markers like tumor necrosis factor-alpha, IL-1, and IL-6 are raised in cohorts who suffered from POCD compared to those who did not show cognitive impairment in the perioperative period in total hip arthroplasties[38]. Elevated levels of specific markers of neuronal damage and repair processes like NSE and S100β were measured by Bu *et al*[29] in their trial. Low regional brain oxygenation and increased brain cellular metabolism as measured by lactate production and glucose utilization rate can also produce neuronal damage[39]. Preventive measures are directed to mitigate these inflammatory processes. External factors are responsible for exaggerated inflammatory processes and steps for neuroprotection to prevent cognitive dysfunction are summarized in Table 1.

GENERAL AND SPECIFIC RISK FACTORS FOR PND AND THE PREVENTIVE MEASURES TO MITIGATE THE INCIDENCE AND SEVERITY OF POCD

There is no strong evidence to support one anesthesia technique over another to prevent POCD. A recent meta-analysis suggested that the addition of regional anesthesia/neuraxial anesthesia to general anesthesia in major noncardiac surgery has decreased the incidence of PND in the first postoperative month compared to those who did not receive any supplemental regional anesthesia[40]. The addition of regional anesthesia techniques decreases pain and perioperative opioid requirements. However, the results have not been consistent in other RCTs[41-43]. Similarly, there is no consistent evidence suggesting total intravenous anesthesia is associated with a lower incidence of delirium than inhalational anesthesia in preventing postoperative delirium in adults after general anesthesia[14,44].

DEX CLINICAL USE IN THE MANAGEMENT OF COGNITIVE DYSFUNCTION

The search for an ideal neuroprotective agent has been very difficult in performing clinical trials due to the heterogeneous patient population, wide range of surgeries, and lack of objective measurement of neuroinflammation and clinical outcome measures. In the last decade, the efficacy of Dex in preventing POCD has been tried in various clinical trials with mixed results. Dex has emerged as an "all-in-one" drug with wide application in the perioperative period. Possible mechanisms by which Dex provides neuroprotection and prevents POCD are: (1) Anti-inflammatory (decrease neuroinflammation); (2) Sympatholytic (decrease circulating catecholamine); (3) Opioid minimizing effect; (4) Analgesia; and (5) Decreased intraoperative volatile anesthetics requirements.

Table 1 The general and specific risk factors for perioperative neurocognitive disorders and the preventive measures to be taken to mitigate the incidence and severity of postoperative cognitive dysfunction

Specific factors	Risk factors	Preventive measures for neuroprotection
Patient-related	Frailty	(1) Multidisciplinary approach; (2) Identification of high-risk patients; (3) Optimization of comorbidities; (4) Establishing baseline cognitive function/dysfunction; (5) Neuropsychiatric/pharmacist consult for alcohol/psychotropic dependence; (6) Consideration of informed consent with patient and family; and (7) Cognition preconditioning
	Age > 65 years	
	Dementia, neurodegenerative disorder	
	Excessive alcohol consumption	
	Polypharmacy including psychotropic drugs	
	Vascular disorders	
	Sleep disorders	
	Diabetes mellitus	
	Prior neuron damage like stroke or traumatic brain injury	
Surgery-related	Type of surgeries: (1) Open cardiac surgery; (2) Invasive cardiac surgery; (3) Major Orthopedic surgery; (4) Head and neck surgery; and (5) Colorectal surgeries	Measures to decrease the duration of surgery
	Increased duration of surgery is associated with increased risk of POCD	Identifying the type and expected duration of surgery
	Postoperative medical and surgical complications	Minimization and early treatment of any postoperative complications
Anesthesia-related	General factors: (1) Excessive depth of anesthesia under GA; (2) Excessive sedation in regional anesthesia; (3) Extremes of blood pressures; (4) Hemodynamic fluctuations; and (5) Cerebral desaturation	(1) Depth of anesthesia monitoring using BIS, entropy; (2) Minimizing excessive sedation; (3) Hemodynamic monitoring and preventing extreme fluctuations from baseline; (4) Cerebral oximetry monitoring in high-risk cases; and (5) Opioid minimizing/sparing techniques
	Specific agents: Benzodiazepines, gabapentinoids, ketamine, opioids, diphenhydramine, metoclopramide, anticholinergics (particularly scopolamine), and diphenhydramine	

BIS: Bispectral index; GA: General anesthesia; POCD: Postoperative cognitive dysfunction.

Bu *et al*[29] measured some important parameters between the two groups (Dex *vs* placebo) to assess the neuroprotective and anti-inflammatory properties of Dex in elderly patients undergoing radical colon cancer surgeries. The use of Dex resulted in decreased levels of NSE and S100β. There were better cerebral regional brain oxygenation measurements at important time points (intubation, extubation, and 30 min after surgical commencement) in the Dex group. The findings of Bu *et al*[29] underscore the potential benefits of using Dex as an adjunct to general anesthesia in elderly patients undergoing major surgeries.

Although current evidence is insufficient to support the routine use of Dex to prevent delirium or other types of postoperative neurocognitive disorders, it aligns with the 2024 Professional Society recommendations that suggest it is reasonable to administer an intraoperative infusion or to continue this infusion into the postoperative period to reduce the incidence of postoperative delirium in high-risk patients[45]. Several studies have indicated that perioperative administration of Dex may mitigate or reduce the incidence of delirium. A 2023 network meta-analysis of randomized trials, which included 18 studies with a total of 2636 patients undergoing cardiac surgery, demonstrated that the administration of Dex in the postoperative period significantly reduced the risk of postoperative delirium when compared with normal saline placebo [odds ratio (OR) = 0.13, 95% confidence interval (CI): 0.03-0.35] or propofol (OR = 0.19, 95%CI: 0.04-0.66)[25]. Similar findings were reported in a 2018 meta-analysis involving patients treated with cardiac surgery[26].

Additionally, a 2018 meta-analysis of randomized trials, which included both cardiac and non-cardiac surgeries, noted a lower incidence of delirium when Dex was administered either intraoperatively or postoperatively compared to no Dex exposure (OR = 0.35, 95%CI: 0.24-0.51; 18 trials, 3309 patients)[27]. Moreover, a 2023 randomized trial involving 732 older adults (aged 65 years or above) undergoing orthopedic lower limb surgery under spinal anesthesia reported a lower incidence of delirium in patients who received Dex sedation during the procedure[28]. It is noteworthy that data are most robust in studies investigating postoperative Dex infusions in intensive care unit settings[14,26-28,46].

Results from the studies on intraoperative administration of Dex are inconsistent, with some data indicating no significant benefit for delirium reduction[47-49]. A multicenter prospective study demonstrated that a continuous infusion of Dex at 0.5 μg/kg/h for 2 h during the intraoperative period did not impact cognitive outcomes at 3 months or 6 months post-surgery, as assessed by multiple neuropsychological tests[48]. In an RCT trial conducted in elderly patients aged ≥ 65 years, Dex was found to have no significant effect on reducing the incidence of POCD at 1 week post-surgery

when compared to propofol. Additionally, no notable difference in the incidence of POCD was observed between the groups at the 1-year follow-up, as evaluated by five neuropsychological test scales other than the MMSE[50].

Additionally, all these trials have various limitations. These studies on Dex include participants with varying baseline characteristics, such as age, comorbidities, and cognitive function. This heterogeneity introduces confounding factors that may obscure the true effect of Dex on PND outcomes. For instance, patients with preexisting cognitive impairment or frailty may respond differently to the drug compared to healthier individuals, making it challenging to generalize findings across diverse populations. The studies reviewed encompass a wide range of surgical procedures, including cardiac, orthopedic, and oncological surgeries. Each type of surgery involves distinct perioperative stressors and inflammatory responses, which could influence the development of PND and the effectiveness of Dex. For example, the inflammatory cascade triggered during cardiac surgery with cardiopulmonary bypass may differ significantly from that in non-cardiac surgeries, potentially altering the efficacy of the drug. The studies employ different dosages and administration protocols for Dex, ranging from intraoperative boluses to continuous perioperative infusions. This variability complicates comparisons and raises questions about the optimal dose and timing to achieve neuroprotective effects while minimizing adverse events. For instance, high doses might increase the risk of bradycardia and hypotension, especially in elderly patients with compromised cardiovascular reserves.

The assessment of PND outcomes varies significantly among studies, with methods including the MMSE, Montreal Cognitive Assessment, and other neuropsychological tools. Additionally, the timing of assessments (*e.g.*, immediate postoperative period *vs* weeks or months later) influences the reported incidence and severity of PND. This inconsistency in outcome measurement limits the comparability of results and the ability to draw definitive conclusions. The lack of standardized protocols across studies contributes to variations in findings. Differences in study design, including sample size, randomization, and control for confounders, further challenge the reliability of the evidence. Methodological rigor, such as multicenter trials with standardized interventions and outcome assessments, is essential to generate more robust and generalizable data. The evidence supporting the use of Dex to prevent other types of PND is also limited[51-53].

While Dex offers significant neuroprotective and anti-inflammatory benefits, its use is not without risks, particularly in elderly patients who often have limited physiological reserves. Common adverse effects include bradycardia and hypotension, which result from its potent sympatholytic and vasodilatory properties. Excessive sedation is another concern, especially when higher doses are used or when combined with other sedatives, potentially delaying postoperative recovery. Furthermore, prolonged use of Dex can lead to rebound hypertension upon discontinuation, and its effects on renal and hepatic function require consideration in patients with organ dysfunction. These risks underscore the need for individualized dosing regimens and vigilant perioperative monitoring to maximize its benefits while minimizing harm.

Dex appears to provide neuroprotective effects, possibly due to its ability to maintain cerebral oxygenation and reduce metabolic stress on the brain. These results align with previous studies that have highlighted the sedative and analgesic properties of Dex, which can help stabilize hemodynamics and reduce the overall need for other anesthetic agents. The reduced incidence of POCD observed in the study by Bu *et al*[29] is particularly noteworthy in mitigating the risk of POCD. Dex not only enhances patient outcomes but also reduces the burden on healthcare systems.

A more thorough grasp of the function of Dex in neuroprotection will also be possible by examining its relative effectiveness in comparison to other pharmaceutical agents or non-pharmacological therapies. The pathophysiology of PND may be better understood and patient selection for the use of Dex may be improved with research examining the discovery and validation of biomarkers for the condition. Finally, to optimize perioperative care strategies, it will be crucial to investigate its long-term effects on cognitive outcomes, particularly in high-risk populations. Standardized dosage schedules and administration procedures catered to various surgical populations ought to be assessed in these studies.

CONCLUSION

This article advocated for the inclusion of Dex in anesthesia protocols for elderly patients undergoing major surgeries like radical colon cancer surgery. Its use not only enhances patient outcomes by mitigating the risk of POCD but also contributes to reducing healthcare costs by facilitating early discharge and minimizing the need for prolonged postoperative care. As such, Dex presents a valuable adjunct in the perioperative management of elderly patients, offering a neuroprotective strategy that aligns with modern enhanced recovery protocols.

FOOTNOTES

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EDITORIAL

Hyperthermia combined with opioid therapy: Enhancing cancer pain management and reducing surgical stress in gastrointestinal cancer patients

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Abstract

In this article, we evaluate the findings of the study by Qian *et al*, which explores the efficacy of combining hyperthermia with opioid therapy for enhanced cancer pain management in patients with middle and late-stage gastrointestinal tumors. The study undertakes a retrospective analysis comparing traditional opioid therapy to an integrated approach of hyperthermia and opioids across 70 patients, highlighting significant benefits in pain control, reduction of opioid dosage, and minimization of adverse reactions. In our article, we not only discuss these findings but also emphasize the broader implications for clinical practice, particularly in enhancing patient outcomes through innovative pain management strategies. We advocate for further research to establish more robust data supporting this approach and to explore the mechanistic insights that enable these benefits. This discussion reflects on the potential paradigm shift in managing debilitating cancer-related pain, urging a reevaluation of current practices to incorporate these findings effectively.

Key Words: Gastrointestinal cancer; Hyperthermia; Opioid therapy; Cancer pain manage-

ment; Surgical stress reduction; Enhanced recovery; Adverse reactions; Pain control

Core Tip: This article highlights a novel combination therapy involving hyperthermia and opioid treatment for managing cancer-related pain in gastrointestinal cancer patients. The approach has shown promising results in enhancing pain control, reducing opioid dosage, and minimizing adverse reactions. The integration of hyperthermia not only improves pain management but also aids in reducing surgical stress and accelerating recovery. The article advocates for further research to fully understand the mechanisms at play and to explore broader clinical applications, potentially setting a new standard in oncological care.

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INTRODUCTION

Cancer-related pain, particularly in patients with advanced gastrointestinal tumors, presents a formidable challenge in oncology. Traditional opioid-based therapies, while effective, are often accompanied by significant drawbacks, including adverse reactions and a compromised immune response[1]. A recent study by Qian *et al*[2], published in the *World Journal of Gastrointestinal Surgery*, introduced an innovative approach that combines hyperthermia with opioid therapy to address these issues. This article explores the implications of their findings, supporting a potential shift in cancer pain management protocols while integrating recent advances and perspectives in the field.

THE STUDY'S CONTRIBUTION TO THE FIELD

Qian *et al*'s study[2] provides compelling evidence that integrating hyperthermia with opioid therapy can significantly improve pain management in patients with gastrointestinal cancer. The key findings include superior pain control, a reduction in opioid dosage, and a shortened postoperative recovery period, all of which are critical for improving patient outcomes. These findings align with the growing body of research that supports the use of multimodal approaches to pain management, particularly in complex cases such as cancer.

RECENT ADVANCES IN THERMAL THERAPY FOR CANCER PAIN CONTROL

Thermal therapy, or hyperthermia, has long been recognized as an adjunct to conventional cancer treatments such as radiation and chemotherapy[3]. However, recent advances have expanded its role, particularly in the management of[4, 5]. These developments have been driven by a deeper understanding of hyperthermia's biological effects and technological innovations that have improved its precision and efficacy[6]. Below, I explore some of the key advances in thermal therapy that have significant implications for cancer pain control.

Enhanced precision and targeting with endogenous field hyperthermia

One of the most significant recent advancements in thermal therapy is the development of endogenous field hyperthermia[7]. Unlike earlier forms of hyperthermia that relied on external heat sources, endogenous field hyperthermia uses electromagnetic fields to generate heat from within the body, directly targeting tumor tissues[8]. This method allows for more precise control of the temperature and duration of heat exposure, minimizing damage to surrounding healthy tissues while maximizing the therapeutic effect on the tumor[6]. Endogenous field hyperthermia has shown promise in selectively raising the temperature of tumor cells to levels that induce apoptosis or necrosis, thereby reducing tumor size and alleviating pressure on surrounding tissues and nerves, which can significantly reduce cancer-related pain[9]. The ability to focus heat on the tumor site reduces the risk of collateral damage to healthy cells, which has been a limitation of earlier hyperthermia techniques. This precision not only enhances the safety profile of hyperthermia but also improves patient comfort during and after treatment[10].

Combination of hyperthermia with nanotechnology

Another groundbreaking development is the integration of hyperthermia with nanotechnology, which has opened new

avenues for cancer pain management[11,12]. Nanoparticles can be engineered to absorb electromagnetic radiation and convert it into heat, thereby providing a highly localized heating effect when exposed to an external energy source such as infrared light or radiofrequency waves[13]. Research has demonstrated that nanoparticles, such as gold or iron oxide, can be delivered to tumor sites where they accumulate[14]. When these nanoparticles are activated by external energy sources, they produce localized hyperthermia that can destroy tumor cells and relieve pain caused by tumor mass effects [15]. In addition to generating heat, nanoparticles can be functionalized to carry chemotherapeutic agents or analgesics directly to the tumor site[16]. This dual functionality not only targets the tumor more effectively but also ensures that pain-relieving medications are concentrated where they are most needed, reducing systemic side effects and improving pain control.

Integration of hyperthermia with radiation therapy

Hyperthermia has been increasingly integrated with radiation therapy, a combination that has been shown to enhance the efficacy of both treatments[17,18]. The thermal effects of hyperthermia can sensitize tumor cells to radiation, making them more susceptible to damage while also alleviating pain through the reduction of tumor burden[19]. In addition to, hyperthermia increases the oxygenation of tumor tissues, which enhances the effectiveness of radiation therapy. This radio sensitizing effect has been particularly beneficial in tumors that are resistant to radiation alone, such as those located in hypoxic or fibrotic environments[20]. As hyperthermia and radiation work together to shrink tumors, the pressure on surrounding nerves and tissues decreases, leading to significant pain relief[21]. This synergistic effect has been documented in various clinical trials, particularly in patients with head and neck cancers, soft tissue sarcomas, and gastrointestinal tumors[3,22].

Advances in thermoablative techniques

Thermoablation, a form of thermal therapy that uses heat to destroy tumor cells, has seen significant advancements in recent years[23]. This technique is particularly useful for managing pain in patients with localized tumors that are difficult to treat with surgery or systemic therapies[24]. Radiofrequency ablation has become a standard treatment for certain types of cancer, particularly liver, lung, and kidney tumors. This technique uses high-frequency electrical currents to generate heat and ablate tumor tissue, providing immediate pain relief by reducing the size of the tumor mass[25,26]. Microwave ablation is another thermoablative technique that has gained traction for its ability to treat larger tumors and those located near critical structures[27]. Microwave ablation uses microwaves to generate heat and induce cell death, and it has been shown to be particularly effective in managing pain associated with bone metastases and soft tissue tumors [28,29].

Immune system modulation through hyperthermia

One of the emerging areas of research in hyperthermia is its potential to modulate the immune system, offering a dual benefit of pain relief and enhanced anti-tumor immunity. Hyperthermia has been shown to increase the expression of heat shock proteins, which play a critical role in immune responses[27]. Heat shock proteins can stimulate the immune system by acting as danger signals that activate dendritic cells and promote the presentation of tumor antigens to T cells [30]. This process not only enhances the immune system's ability to target and destroy tumor cells but also contributes to the reduction of pain by diminishing the tumor's inflammatory environment. Besides, there is growing interest in combining hyperthermia with immunotherapies, such as checkpoint inhibitors, to enhance their effectiveness[31]. Hyperthermia can increase the infiltration of immune cells into tumors, potentially overcoming resistance to immunotherapy and providing additional pain relief through the reduction of tumor-induced inflammation[32].

Clinical trials and evidence-based practices

As thermal therapy continues to evolve, numerous clinical trials have been conducted to assess its efficacy in cancer pain management. These trials have provided a growing body of evidence supporting the use of hyperthermia in combination with other treatments[18]. Large-scale clinical trials have demonstrated the benefits of adding hyperthermia to standard cancer treatments, particularly in reducing pain and improving quality of life. For example, a phase III trial in patients with recurrent breast cancer found that the addition of hyperthermia to radiation therapy significantly improved pain control and local tumor response rates[33]. Based on the results of these trials, professional organizations have begun to develop guidelines and protocols for the use of hyperthermia in clinical practice[34]. These guidelines emphasize the importance of patient selection, treatment planning, and the integration of hyperthermia with multimodal pain management strategies.

REDUCING SURGICAL STRESS AND IMPROVING RECOVERY

The benefits of combining hyperthermia with opioids extend beyond pain management to the realm of surgical stress reduction. Surgical interventions, particularly in advanced cancer cases, are associated with significant physiological stress, which can impair recovery and prolong hospitalization. Hyperthermia has been shown to reduce markers of surgical stress, such as cortisol and C-reactive protein, leading to faster recovery times and shorter hospital stays[35]. Recent studies have also explored the timing of hyperthermia in relation to surgery, suggesting that preoperative hyperthermia can prime the immune system and reduce surgical stress, while postoperative hyperthermia can enhance recovery by reducing inflammation and promoting tissue healing[36]. This makes hyperthermia a versatile tool in the perioperative management of cancer patients, with the potential to improve both immediate and long-term outcomes[37].

BROADER IMPLICATIONS FOR CLINICAL PRACTICE

The integration of hyperthermia with opioid therapy could represent a paradigm shift in the management of cancer pain, particularly in patients with gastrointestinal tumors. The benefits observed in this study - enhanced pain control, reduced reliance on opioids, and improved postoperative recovery - suggest that this approach could be a valuable addition to existing pain management protocols. By improving pain management and reducing the physiological stress associated with surgery, this combined approach could significantly enhance patient outcomes, leading to better quality of life and potentially even improved survival rates. The reduced need for opioids and faster recovery times could also translate into lower healthcare costs, with shorter hospital stays and fewer complications.

STUDY LIMITATIONS AND CHALLENGES

While Qian *et al*'s study[2] provides compelling evidence that integrating hyperthermia with opioid therapy can significantly enhance pain management in patients with gastrointestinal cancer. However, several notable limitations should be acknowledged and addressed in future research. First, the study's sample size is relatively small. Although the study included data from 70 patients, this limited sample size may not adequately represent the diverse populations of gastrointestinal cancer patients. Expanding the sample size in future studies to encompass a broader range of gastrointestinal cancer subtypes is essential to enhance the generalizability and reliability of the findings. Second, the study provides insufficient exploration of the underlying mechanisms. While Qian *et al*[2] primarily focused on clinical outcomes, there is limited investigation into the molecular and cellular mechanisms underlying the combined effects of hyperthermia and opioid therapy. Future research should prioritize elucidating these mechanisms to better understand the therapeutic advantages and potential risks associated with this combination therapy. Third, the retrospective nature of the study introduces potential biases. Retrospective studies are prone to selection bias and incomplete data, which can compromise the reliability and generalizability of the results. To address these issues, prospective randomized controlled trials should be conducted. Such studies will provide more robust evidence, reduce biases, and enhance the scientific validity of the findings, ultimately supporting more reliable clinical applications. By addressing these limitations, future research can build upon the promising findings of Qian *et al*'s study[2] and contribute to the development of more effective and evidence-based pain management strategies for patients with gastrointestinal cancer.

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

As the integration of hyperthermia with opioid therapy continues to show promise in the management of cancer pain and surgical stress, several key areas of future research and development need to be addressed to fully harness the potential of this combined approach. Below, I outline some of the most critical directions for future research.

Understanding the mechanisms of action

While current studies have demonstrated the efficacy of hyperthermia in enhancing pain control and reducing surgical stress, the precise mechanisms underlying these effects remain incompletely understood. Future research should focus on elucidating the biological and molecular pathways through which hyperthermia interacts with opioid drugs and affects tumor biology, pain perception, and immune function[37].

Tumor microenvironment and hyperthermia: One area of interest is how hyperthermia modulates the tumor microenvironment to enhance the permeability of tumor cells and surrounding tissues, potentially improving drug delivery and efficacy[38]. Understanding these interactions could lead to the development of more targeted and effective hyperthermia protocols, particularly in combination with other therapeutic modalities.

Pain pathways and sensory nerve modulation: Another critical research direction is to explore how hyperthermia influences the neural pathways associated with pain perception. Investigating the impact of thermal therapy on sensory nerve excitability and pain signaling could uncover new strategies for modulating pain responses in cancer patients.

Immune modulation: Given that hyperthermia has been shown to enhance immune responses, it is important to understand how these effects can be optimized in the context of cancer therapy. Research should focus on how hyperthermia-induced changes in immune cell activity can counteract the immunosuppressive effects of opioids and contribute to tumor control.

Personalized medicine and biomarker development

As with many cancer therapies, the response to hyperthermia and opioid treatment can vary significantly among patients. To maximize the efficacy of this combined approach, future research should aim to identify biomarkers that can predict patient response to therapy. By analyzing the genetic and protein expression profiles of patients, researchers may be able to identify specific markers that indicate a higher likelihood of benefiting from hyperthermia and opioid combination therapy. This approach could lead to more personalized treatment plans, tailored to the individual characteristics of each patient's cancer. Developing predictive models that incorporate patient-specific data (*e.g.*, tumor type, genetic markers, immune status) could help clinicians determine the most effective treatment strategies. These models

could be used to guide decisions on the use of hyperthermia, optimal dosing of opioids, and the timing of combined therapies.

Expanding the scope of application

While the current focus of research has been on gastrointestinal cancers, there is significant potential for expanding the application of hyperthermia and opioid combination therapy to other types of cancer. Future studies should explore the efficacy of this approach in cancers that are similarly associated with high levels of pain and surgical stress.

Head and neck cancers: These cancers often involve complex pain management challenges due to their location and the involvement of multiple nerves[39]. Hyperthermia could offer a non-invasive means of enhancing pain control and reducing the side effects of opioid therapy.

Sarcomas and bone metastases: These cancers frequently result in severe pain due to bone involvement and metastasis. Hyperthermia, by enhancing local blood flow and reducing tumor pressure on surrounding tissues, could be particularly beneficial in these cases[40].

Lung and breast cancers: Exploring the use of hyperthermia in conjunction with opioids in lung and breast cancer could provide insights into managing pain associated with large tumor masses and widespread metastasis[41,42].

Integration with emerging therapies

The field of oncology is rapidly evolving, with new therapies and treatment modalities being developed at an unprecedented pace. There is significant potential for integrating hyperthermia and opioid therapy with these emerging treatments to enhance overall patient outcomes. As immunotherapy becomes a cornerstone of cancer treatment, research should investigate how hyperthermia can enhance the immune system's response to tumors when combined with checkpoint inhibitors or other immunotherapeutic agents[43]. Hyperthermia may also be used to improve the delivery and effectiveness of targeted therapies, particularly in tumors that are resistant to conventional treatments. Studies could explore how hyperthermia-induced changes in tumor vascularization and cell membrane permeability affect the uptake of targeted drugs. Given the established role of hyperthermia in sensitizing tumors to radiation, further research is needed to optimize protocols that combine hyperthermia with radiotherapy in a way that minimizes damage to healthy tissues while maximizing tumor control.

Long-term outcomes and survivorship

While much of the current research focuses on immediate pain relief and surgical outcomes, there is a pressing need to explore the long-term effects of hyperthermia combined with opioid therapy.

Survival and disease progression: Investigating whether the combination of hyperthermia and opioids has any impact on overall survival rates and disease progression in cancer patients. This research could help determine whether the approach not only improves quality of life but also contributes to extending life expectancy.

Quality of life and functional recovery: Longitudinal studies should assess the impact of this combined therapy on patients' long-term quality of life, including their ability to return to normal activities and the degree of chronic pain experienced post-treatment.

Recurrence rates: Understanding whether the use of hyperthermia and opioids affects the likelihood of cancer recurrence could provide important insights into the potential for this therapy to alter the long-term trajectory of the disease.

CONCLUSION

The combination of hyperthermia and opioids represents a promising advancement in the management of cancer-related pain and surgical stress, particularly for patients with advanced gastrointestinal cancers. The findings of Qian *et al*[2] provide a strong foundation for this approach, highlighting its potential to improve pain control, reduce opioid reliance, and enhance recovery. As research in this area continues to evolve, there is hope that this innovative strategy will lead to a new standard of care in oncology, offering patients better outcomes and a higher quality of life. However, further research is essential to fully realize the potential of this approach, particularly in understanding the underlying mechanisms, optimizing treatment protocols, and expanding its application to other cancer types.

FOOTNOTES

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EDITORIAL

Risk and management of adverse events in minimally invasive esophagectomy

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Abstract

Minimally invasive esophagectomy (MIE) has transformed esophageal surgery by reducing morbidity, accelerating recovery, and improving postoperative outcomes compared to traditional open esophagectomy. By utilizing techniques such as laparoscopic, thoracoscopic, and robotic-assisted approaches, MIE mini-mizes surgical trauma while maintaining oncological thoroughness. However, it also presents unique challenges, including risks of complications such as ana-stomotic leakage, pulmonary complications, and atrial fibrillation. Zhong *et al* developed and validated a risk stratification model for predicting surgical adverse events after MIE, enhancing preoperative assessment and patient management. This editorial further examines the advantages of MIE, its comparable oncological and long-term outcomes, as well as the incidence and contributing factors of post-operative complications. Emerging technologies, including machine learning models, intraoperative nerve monitoring, and robotic-assisted surgery, are high-lighted as innovative solutions for risk prediction and prevention. Strategies such as enhanced recovery after surgery protocols and multidisciplinary collaboration are emphasized for their critical roles in minimizing complications and optimizing patient outcomes. By addressing these aspects, this editorial provides guidance to surgical teams in maximizing the benefits of MIE while effectively managing its associated risks.

Key Words: Minimally invasive esophagectomy; Anastomotic leakage; Enhanced recovery after surgery; Robotic-assisted surgery; Surgical adverse events

Core Tip: Minimally invasive esophagectomy (MIE) offers significant benefits, including reduced morbidity, faster recovery, and comparable oncological outcomes to open esophagectomy. This study highlights key complications such as anastomotic leakage, pulmonary issues, and atrial fibrillation, while identifying risk factors including high body mass index and comorbidities. Emerging technologies like machine learning, intraoperative nerve monitoring, and robotic-assisted surgery enhance risk prediction and surgical precision. Strategies like enhanced recovery after surgery protocols and multidisciplinary approaches are emphasized for their role in minimizing complications and optimizing recovery. This editorial guides surgical teams in maximizing MIE's benefits while effectively managing associated risks.

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INTRODUCTION

Minimally invasive esophagectomy (MIE) has transformed esophageal surgery by offering significant benefits, including reduced morbidity, faster recovery, and improved postoperative outcomes compared to traditional open esophagectomy (OE)[1]. These advantages are achieved through techniques such as laparoscopic, thoracoscopic, and robotic-assisted approaches, which minimize surgical trauma while maintaining oncological thoroughness[2]. However, MIE is not without challenges, as it presents unique risks and technical complexities.

Studies from multiple regions and healthcare systems consistently demonstrate that MIE offers significant reductions in postoperative pulmonary complications and wound infections compared to OE, with complication rates lowered by up to 4.29 times in some high-risk populations, such as the elderly and patients with preexisting pulmonary conditions[3,4]. Moreover, region-specific analyses indicate that high-volume centers consistently achieve better outcomes with MIE, highlighting the importance of institutional expertise. For example, a multicenter study from Europe reported significantly shorter hospital stays and reduced mortality rates with MIE, while a study from Asia highlighted its applicability even in low-resource settings with proper training and technology[5,6].

In addition to these benefits, MIE demonstrates comparable oncological outcomes to OE, including similar lymph node harvest rates and five-year survival outcomes. These results underscore the reliability of MIE as a cancer treatment modality. Furthermore, patients undergoing MIE experience faster recovery times, enhanced quality of life, and lower healthcare costs due to reduced hospital stays and fewer postoperative complications.

This editorial provides an in-depth exploration of the benefits of MIE, the incidence and causes of complications, the role of emerging technologies in risk reduction, and strategies for optimizing patient outcomes. By addressing these aspects, the editorial aims to guide surgical teams in maximizing the benefits of MIE while effectively managing its associated risks.

BENEFITS OF MIE

Reduced postoperative complications

MIE substantially lowers the risk of postoperative complications compared to OE, particularly for pulmonary and wound-related issues (Table 1). Pulmonary complications, a leading concern in esophageal surgery, are significantly reduced with MIE. This is attributed to the smaller thoracic incisions, which minimize disruption to the chest wall and respiratory mechanics. Studies indicate that MIE reduces the likelihood of pulmonary complications by up to 4.29 times compared to OE[7]. This advantage is especially beneficial for high-risk populations, such as elderly patients and those with preexisting pulmonary conditions, who otherwise face heightened risks of pneumonia, atelectasis, and respiratory failure after surgery[3,5].

Additionally, wound infections and other surgical site complications are significantly less frequent with MIE. The smaller incisions required for MIE reduce the risk of bacterial contamination, promote faster healing, and lower the odds ratio for wound infections to 0.31 compared to OE[4]. The cumulative reduction in complications leads to improved overall outcomes and a smoother recovery process.

Enhanced recovery and shorter hospital stays

Patients undergoing MIE consistently experience shorter hospital stays compared to those undergoing OE (Table 1). This is due to the minimally invasive nature of MIE, which reduces intraoperative blood loss, tissue trauma, and postoperative pain. A meta-analysis reported that MIE patients had hospital stays that were several days shorter on average compared to OE patients, reflecting a more efficient recovery process[8]. The quicker return to bowel function and reduced reliance on intensive postoperative monitoring further contribute to reduced hospitalization durations.

Moreover, MIE allows for earlier mobilization and resumption of daily activities. Patients report faster recovery timelines, with earlier initiation of oral diets and ambulation, compared to the prolonged recovery associated with OE[9].

Table 1 Comparison of key outcomes between minimally invasive esophagectomy and open esophagectomy

Parameter	Minimally invasive esophagectomy	Open esophagectomy
Pulmonary complications	Lower incidence due to reduced surgical trauma and improved respiratory mechanics	Higher incidence due to larger thoracic incisions and greater disruption of respiratory structures
Anastomotic leak rate	Comparable rates with optimized techniques and better visualization during surgery	Slightly higher rates in some studies due to technical challenges with large incisions
Wound infections	Significantly reduced risk due to smaller incision size and less exposure to contamination	Higher risk associated with larger incision size and longer healing times
Postoperative recovery	Faster recovery with shorter hospital stays and quicker return to daily activities	Slower recovery due to greater surgical stress and longer hospitalization
Oncological outcomes	Comparable lymph node harvest and survival rates	Equivalent oncological efficacy with traditional surgical thoroughness
Technological requirements	Requires advanced equipment and surgeon training (*e.g.*, robotic systems, IONM)	Requires fewer technological resources but depends heavily on surgical expertise

IONM: Intraoperative nerve monitoring.

These benefits not only improve patient quality of life but also reduce healthcare costs and resource utilization.

Comparable oncological and long-term outcomes

MIE has demonstrated oncological outcomes comparable to OE, ensuring that its minimally invasive nature does not compromise cancer treatment efficacy (Table 1). The number of lymph nodes harvested during MIE is equivalent to that in OE, maintaining the surgical thoroughness required for accurate staging and effective treatment[6]. Five-year survival rates for MIE patients are also comparable to those for OE patients, indicating its reliability as a cancer treatment modality[10].

In terms of long-term outcomes, MIE offers additional advantages due to its association with a reduced surgical stress response. Patients undergoing MIE exhibit better-preserved immune function and superior intestinal barrier integrity, which contribute to improved long-term survival and reduced postoperative morbidity[9,11].

INCIDENCE AND CAUSES OF POSTOPERATIVE COMPLICATIONS

Common complications

Despite its benefits, MIE is associated with certain complications that can impact recovery and long-term outcomes. Anastomotic leaks, pulmonary complications, and atrial fibrillation (AF) are the most frequently reported issues. Anastomotic leaks, occurring in 7.7%-14.8% of cases, are critical complications that increase the risk of sepsis and negatively affect survival rates[12,13]. Pulmonary complications, such as pneumonia and respiratory failure, are also common, although their incidence is lower in MIE compared to OE[14].

Postoperative AF is observed in approximately 25.6% of MIE patients, contributing to extended hospital stays and an increased risk of thromboembolic events. While transient in most cases, AF requires prompt management to prevent further complications[15].

Contributing factors

Multiple factors influence the incidence of complications in MIE, including patient characteristics, surgical techniques, and institutional expertise. High body mass index and preexisting conditions such as diabetes or chronic obstructive pulmonary disease are significant risk factors that predispose patients to complications like anastomotic leaks and respiratory issues[16].

In addition to comorbidities, individual patient characteristics such as age, gender, and genetic predispositions also play a critical role in determining outcomes and complications in MIE. For example, elderly patients often face increased risks of postoperative pulmonary complications due to reduced respiratory reserve and slower recovery times. Male patients have been noted in some studies to have a higher incidence of anastomotic leaks compared to females, potentially linked to anatomical or hormonal differences. Genetic predispositions, such as variations in inflammatory or healing-related genes, may also impact the likelihood of complications like sepsis or delayed wound healing. Recognizing these individual factors is essential for tailoring preoperative risk assessments and postoperative management strategies.

To mitigate these risks, individualized treatment strategies should be implemented. For elderly patients, prehabilitation programs focusing on improving physical fitness and optimizing nutrition can enhance surgical outcomes. Smokers may benefit from preoperative smoking cessation programs, which have been shown to significantly reduce pulmonary complications. Patients with complex comorbidities require a multidisciplinary approach, incorporating cardiology, pulmonology, and nutritional expertise to ensure comprehensive risk management and support throughout the perioperative period. By addressing the unique needs of these patient groups, surgical teams can improve the safety

and effectiveness of MIE.

The technical complexity of MIE, particularly in performing intrathoracic anastomosis, adds to the risk. Studies have shown that less experienced surgical teams report higher rates of leaks and other complications[17]. In contrast, high-volume centers with experienced surgical teams consistently achieve better outcomes, highlighting the importance of institutional expertise in minimizing complications[18].

EMERGING TECHNOLOGIES FOR RISK PREDICTION AND PREVENTION

Predictive tools and machine learning

Zhong *et al*[19] developed and validated a risk stratification model for predicting surgical adverse events after MIE, significantly improving preoperative assessment and patient management. This model serves as a foundation for developing tools that identify high-risk patients and enable tailored perioperative strategies to minimize complications.

Machine learning (ML) models have further advanced these efforts by integrating clinical and imaging data to generate risk predictions with high accuracy. For example, neural networks and support vector machines are commonly used ML algorithms that analyze large datasets, identifying complex patterns and correlations that traditional statistical methods may overlook. One study demonstrated that advanced ML models achieved an area under the ROC curve of 0.87 for predicting anastomotic leaks, outperforming conventional predictive models[20].

Despite these promising results, the clinical adoption of ML models faces several challenges. Firstly, the quality and consistency of input data are critical for model accuracy, and discrepancies in data collection across institutions can limit generalizability. Secondly, integrating ML models into clinical workflows requires user-friendly interfaces and seamless interoperability with existing electronic health record systems, which often necessitate significant technological investment. Thirdly, the "black box" nature of some ML algorithms raises concerns about interpretability, making clinicians hesitant to rely solely on these tools for decision-making. Addressing these issues through improved data standardization, user-centered design, and transparent algorithm development will be essential for broader implementation.

Despite these challenges, ML models offer distinct advantages in MIE. By providing real-time risk assessments, these tools enable proactive interventions that can prevent complications and optimize patient outcomes. Furthermore, the ability of ML to analyze high-dimensional data makes it particularly suited for personalized risk stratification, allowing for tailored surgical and postoperative strategies based on individual patient profiles.

Intraoperative technologies

Intraoperative nerve monitoring (IONM) is a technique used during surgery to reduce the risk of nerve damage by providing real-time feedback on the functional integrity of nerves. During MIE, IONM is employed to monitor the recurrent laryngeal nerve, which is susceptible to injury during esophagectomy. This technology uses electrical stimulation to detect nerve responses, enabling surgeons to avoid accidental damage. Studies have shown that the use of IONM significantly decreases the incidence of vocal cord paralysis and respiratory complications, enhancing surgical safety and patient outcomes[21]. AI-assisted navigation systems further support surgical precision by providing real-time identification of critical structures, reducing intraoperative risks[22].

Robotic-assisted surgery

Robotic-assisted surgery (RAS) is a cutting-edge technology that enhances surgical precision, dexterity, and visualization through robotic systems controlled by surgeons. In the context of MIE, RAS offers unmatched accuracy during complex procedures, such as intrathoracic anastomosis, by providing a magnified 3D view of the surgical field and enabling precise instrument movement. This technology is particularly beneficial in challenging cases where traditional laparoscopic techniques may be less effective. While robotic systems involve higher upfront costs and training requirements, they have demonstrated improved patient outcomes, such as reduced postoperative complications and shorter recovery times[23].

Despite these advantages, the long-term effectiveness and cost-effectiveness of RAMIE and other emerging technologies require further exploration. For example, while RAMIE has demonstrated reduced complication rates in high-volume centers, its outcomes in low-resource settings or smaller institutions remain underreported. The high initial costs of robotic systems and the associated training requirements also pose challenges to their widespread adoption. Moreover, data on the long-term oncological outcomes of RAS compared to traditional MIE approaches is still limited, particularly in diverse healthcare settings. Addressing these gaps through multicenter studies and cost-benefit analyses will provide valuable insights into the broader applicability and sustainability of these technologies.

STRATEGIES FOR PREVENTION AND MANAGEMENT

Prevention strategies

Enhanced recovery after surgery (ERAS) protocols are evidence-based perioperative care pathways designed to improve surgical outcomes and accelerate patient recovery. In the context of MIE, ERAS protocols include key elements such as preoperative patient education, optimized nutritional support, multimodal pain management, and early mobilization. These measures collectively reduce surgical stress, shorten hospital stays, and minimize complications. For instance,

prehabilitation programs focusing on improving patients' physical fitness and respiratory function before surgery have been shown to reduce postoperative pulmonary complications. Early initiation of oral nutrition postoperatively supports faster recovery of gastrointestinal function, while structured pain management strategies limit the use of opioids, thereby reducing the risk of respiratory depression. ERAS has been widely adopted in high-volume centers, demonstrating a significant reduction in morbidity and improved overall recovery trajectories for MIE patients[4].

Effective management

Prompt detection and management of complications are critical for improving outcomes. Early identification of anastomotic leaks through routine contrast studies allows for timely intervention, either through endoscopic or surgical means. Pulmonary complications can be mitigated with aggressive physiotherapy, respiratory support, and careful monitoring[18].

CONCLUSION

MIE offers significant advantages over traditional open surgery, including reduced complications, faster recovery, and comparable oncological outcomes. However, its success requires meticulous planning, advanced technology, and skilled surgical teams. Emerging tools, such as ML, IONM, and RAS, are transforming risk prediction and complication management, while multidisciplinary approaches and standardized care pathways enhance patient outcomes. To further optimize results, future research should focus on how patient-specific factors, such as age, comorbidities, and genetic predispositions, influence complications. These insights can enable personalized treatment strategies and enhance decision-making. Additionally, multicenter studies and cost-benefit analyses are necessary to evaluate the feasibility and long-term effectiveness of technologies like RAS and AI in diverse healthcare settings. Clinicians are encouraged to integrate advanced tools and tailored protocols to address individual risks, reduce technical complexity, and improve outcomes. Training programs should emphasize robotic and AI-assisted techniques to ensure safe adoption of emerging innovations. Refining ERAS protocols and fostering collaboration among specialists are crucial for optimizing perioperative care, particularly for high-risk populations. As technology evolves, ongoing research and education will be essential to expand access to MIE and maximize its benefits for all patients.

FOOTNOTES

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MINIREVIEWS

Application progress of early nutrition intervention in patients with hepatocellular carcinoma after liver transplantation

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Abstract

Liver transplantation, as an effective therapy for patients with liver cancer, plays an important role in improving the quality of life of patients. However, the complexity and trauma of liver transplantation can easily lead to the occurrence of malnutrition in patients, and then increase the risk of postoperative complications, which has aroused widespread clinical attention. Reasonable nutritional support can not only maintain the stability of the body's internal environment, reduce the occurrence of complications, but also promote the recovery of liver and other organ functions. In recent years, with the in-depth understanding of nutritional metabolism after liver transplantation, the application of enteral nutrition and parenteral nutrition in nutritional support after liver transplantation has been increasingly extensive and achieved remarkable results. This paper discusses the effect of early postoperative nutritional intervention on patients with liver cancer and liver transplantation, and combined with its mechanism of action, can better understand the effectiveness of intervention, and provide reference for the development of scientific and reasonable nutritional support programs in clinical practice.

Key Words: Liver cancer; Liver transplantation; Postoperative intervention; Early nutrition; Research progress; Summarize

Core Tip: This paper discusses the effect of early postoperative nutritional intervention on patients with liver cancer and liver transplantation, and combined with its mechanism of action, can better understand the effectiveness of intervention, and provide reference for the development of scientific and reasonable nutritional support programs in clinical practice.

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INTRODUCTION

As a highly malignant tumor of the digestive system, liver cancer has a hidden onset, rapid development and high degree of malignancy, which often leads to the diagnosis of patients in the middle and late stage. For these patients, liver transplantation, as an effective treatment, can significantly prolong the survival of patients and improve their quality of life. However, liver transplant patients often have a severely impaired liver function and are unable to compensate themselves before undergoing surgery[1]. At the same time, many uncertain factors such as the trauma of the operation itself and the anesthesia treatment during the operation will further aggravate the metabolic pressure of the body, resulting in insufficient nutrition of the patients. If timely intervention measures are not taken, patients will not only face significant weight loss, hypoproteinemia, but also lead to severe consequences such as cachexia, which to some extent seriously affect the recovery of patients' liver function after surgery. Therefore, many domestic authoritative experts have reached a consensus and advocated the implementation of early and active nutritional support strategies for patients after liver transplantation[2].

With the rapid development of nutrition science, clinical medicine and surgical technology, the field of postoperative nutrition intervention has also made remarkable breakthroughs and progress. From the previous parenteral nutrition auxiliary means, the gradual transition to the popularization and application of enteral nutrition, and then to the customization of personalized nutrition plans, the nutrition intervention strategy has been further improved[3]. On the one hand, this series of development has built a more scientific nutritional security system for liver cancer patients with liver transplantation, and on the other hand, it also provides a new perspective and way to promote the postoperative recovery process and optimize the quality of life of patients. Based on this, this paper aims to review the nutritional status of patients with liver cancer and the influence of nutritional intervention on liver transplantation, focusing on the mechanism of nutritional intervention in improving the survival rate of patients with liver cancer and liver transplantation, reducing complications, and promoting organ function recovery, in order to provide theoretical basis and practical guidance for the postoperative management of liver cancer and liver transplantation.

ANALYSIS OF NUTRITIONAL STATUS AND POSTOPERATIVE EFFECTS OF LIVER CANCER

Nutritional status and influencing factors of patients with liver cancer

According to relevant studies, liver (Figure 1) is the main metabolic organ of the human body, and its lesions will inevitably increase the risk of malnutrition in patients[4]. Stachowska *et al*[5] reported in a meta-analysis that fiber supplementation was associated with favorable changes in body mass index (BMI), insulin homeostasis, and liver-related biomarkers in patients with nonalcoholic liver disease. Moreover, Lai *et al*[6] found that the severity of cirrhosis was related to the decreased activity of glutathione and its related enzymes. Among the global malignant tumors, liver cancer is the second deadliest, and the pathogenesis of this disease involves the individual health status of patients, environmental exposure and other aspects. Studies have revealed that the main reasons promoting the occurrence of liver cancer involve obesity and type 2 diabetes, *etc.*, and after further investigation, it is found that nutrition status can become a key factor affecting the tumor process to a certain extent, especially in patients with advanced malignant tumors[7]. Therefore, the nutritional status of patients with malignant tumors has been paid more and more attention by clinicians. Zhang *et al*[8] found in their study that the risk of malnutrition was significantly higher in liver cancer patients receiving transarterial chemoembolization (TACE) treatment, and the risk of malnutrition was significantly positively correlated with their symptom groups. At the same time, studies have found that with the increasing age of patients, their liver function gradually declines, which, coupled with chronic diseases, may cause malnutrition to a certain extent[9]. In addition, in the study of Xi *et al*[10], it was further found that the progression of tumor-node-metastasis stages, the severity of anemia and the activity status of viral hepatitis B all affected the digestive and absorption functions of patients to varying degrees, thus further accelerating the occurrence of malnutrition in tumor patients.

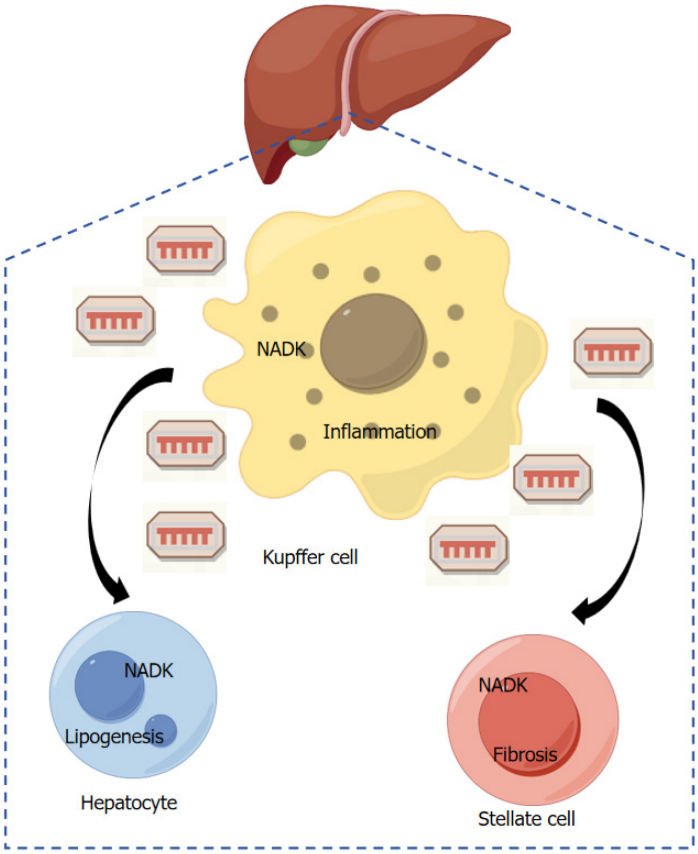

Figure 1 Anatomical microstructure of liver. NAD kinase plays a role in the development of inflammation and liver fibrosis by regulating metabolic and antioxidant mechanisms in the liver. NADK: NAD kinase.

Application value of nutritional intervention in patients with liver cancer after surgery

Studies have shown that stress conditions such as anesthesia and surgical trauma will trigger the body to enter a highly decomposed abnormal metabolic state, among which postoperative insulin resistance is particularly significant, which not only limits the effective use of glucose to a certain extent, but also may lead to a series of metabolic disorders. Thus, the malnutrition of patients is further aggravated and their liver function is seriously damaged[11]. The core of individualized nutrition nursing strategy is to accurately assess the nutritional risk of patients in advance, and comprehensively consider their current nutritional status, personal eating habits and energy needs and other factors, so as to develop targeted diet management programs for them. To some extent, this intervention can effectively improve the nutritional status of patients while at the same time, further promote the overall recovery process of patients[12].

Menozzi *et al*[13] conducted structured interviews with pancreatic cancer surgery patients by means of a 24-hour dietary recall aimed at evaluating the intake of all foods, beverages, and oral nutritional supplements consumed in the last 24 hours, in conjunction with muscle mass measurements to provide a comprehensive nutritional assessment for pancreatic surgery. This study points to the importance of a multidimensional, comprehensive preoperative nutritional assessment and appropriate perioperative nutritional interventions for patients undergoing major cancer surgery in improving tolerance and clinical outcomes of antitumor therapy. Personalized nutritional care played an active role in patients undergoing hepatectomy for hepatocellular carcinoma. It can not only significantly improve the nutritional status of patients to a certain extent, but also promote the metabolism and absorption efficiency of nutrients, thus further enhancing the immune function of patients and conducive to postoperative rehabilitation. At the same time, Sun *et al*[14] used patient subjective global assessment to develop a personalized nutritional intervention plan and selection of nutritional pathways after TACE for hepatocellular carcinoma. Patients were given oral nutritional solution for energy supplementation or intravenous nutrition for energy supplementation as needed with close monitoring of nutritional risk and electrolyte changes, and it was found that the incidence of gastrointestinal complications as well as electrolyte disorders were significantly reduced in the nutritional intervention group. The study concluded that for elderly patients with primary liver cancer, early enteral nutritional support was provided to them after TACE, and the results showed that this measure effectively improved the nutritional status of the patients, and also enhanced the liver function and immune function of the patients to a certain extent, which ultimately improved the prognosis of the patients. In addition, other studies have found that preoperative nutritional risk screening (NRS) and targeted nutritional supplementation based on the assessment results can, on the one hand, successfully solve the problem of nutritional imbalance[15]; on the other hand, postoperative complications can be significantly reduced, thus minimizing the length of hospitalization and enabling patients to recover more quickly. In addition, Yap *et al*[16] also confirmed through systematic analysis that perioperative nutritional intervention could effectively reduce postoperative infection, ascites, length of hospital stay, and increase body weight in patients undergoing hepatocellular cancer resection.

NUTRITION RELATED CLINICAL ASSESSMENT METHODS AND THEIR APPLICATION IN CANCER PATIENTS

Nutrition-related measurement indexes

Anthropometric indicators: When evaluating the physical condition of liver transplant candidates, BMI, upper arm circumference, hand grip strength and other indicators should be measured, and effective comprehensive evaluation should be carried out[17]. However, for most patients, these indicators may interfere with the measurement results due to the presence of peripheral edema and abdominal fluid. The accuracy of BMI in cancer patients may be reduced, so the accuracy of BMI can be improved to a certain extent by scientifically estimating and subtracting the amount of abdominal fluid and other body fluid accumulation to correct BMI value[18]. At the same time, other parameters such as upper arm circumference also serve as an effective basis for assessing the nutritional status of patients. In the aspect of assessing fat reserve and consumption, triceps skin fold thickness is mainly used to judge, and its change can indirectly reflect the metabolic status of the body to a certain extent[19]. In the study of Chong *et al*[20], it was found that skeletal muscle fluctuations occurred in liver transplant patients during the perioperative period. Meanwhile, 30% to 70% of liver transplant candidates were found to have decreased muscle mass and function. Studies have found that for liver transplant recipients, lower muscle mass will not only increase the incidence of complications, but also prolong the duration of intensive care unit stay and the need for mechanical ventilation, and may also lead to a decrease in survival [21]. Luo *et al*[22] introduced the concept of "BMI of abdominal effusion", which dynamically adjusts the critical value of BMI mainly according to the severity of abdominal effusion. Compared with traditional BMI, it is more reliable in assessing patients' malnutrition. In addition, in terms of upper body strength, hand grip strength has been recognized as an effective means of identifying patients with potentially high risk of complications and, to a certain extent, can be a unique predictor of assessing the likelihood of developing major complications in malnourished patients with cirrhosis over the next year.

Biochemical indexes: In the liver, a variety of key plasma proteins such as albumin, retinol-binding protein and enzymes involved in creatinine metabolism can be synthesized, and in this process, they are more susceptible to changes in liver health status and inflammatory response[23]. Therefore, serum albumin concentration and 24-hour urinary creatinine output are important indicators for evaluating nutritional status and predicting prognosis of liver transplant recipients to some extent. Albumin is a core indicator of protein reserve and liver function in the body, among which a low serum albumin level is widely regarded as a key factor to increase the risk of postoperative infection and reduce the survival rate[24]. Creatinine, as a byproduct of muscle metabolism, is produced at a relatively constant rate and is regulated by specific enzymes synthesized by the liver, thus further establishing a link with liver function. In addition, the decrease of 24-hour urinary creatinine excretion, which is an effective indicator for evaluating muscle mass, not only predicts a higher risk of death in patients to a certain extent, but also increases the possibility of transplant failure[25]. Therefore, by monitoring the serum albumin concentration and 24-hour urinary creatinine excretion during the perioperative period, the nutrition and health status of liver transplant recipients can be more comprehensively evaluated, which can further provide data support for the development of personalized nutrition intervention plans.

Biological resistance analysis: Bioelectrical impedance analysis (BIA) technology, as a convenient and safe detection method, is mainly used to measure the body's reactance and resistance, so as to accurately reveal the body's fat mass, somatic cell mass, phase angle and other key indicators[26]. As a core factor, phase angle is often recommended to be measured on the arm and thigh of patients[27]. Cereda *et al*[28] showed in related studies that BIA showed significant advantages in evaluating nutritional status and predicting survival in cancer patients. Moreover, Wang *et al*[29] believed that in the analysis of lung cancer patients, phase angle had higher predictive efficacy than albumin, transferrin and other indicators. At the same time, patients with low preoperative phase angle will not only suffer severe infection after surgery, but also significantly increase the risk of poor prognosis. In addition, phase angle also has the potential of preoperative volume assessment. On the one hand, accurate assessment can reduce blood loss to a certain extent during hepatectomy, and on the other hand, improve surgical safety[30]. Although BIA has a high accuracy in body composition analysis, pathological conditions such as edema and abdominal effusion may interfere with its measurement results, and the detection cost and professional equipment demand of this technology are high[31], so its clinical application is limited to a certain extent.

Nutritional assessment tools

NRS 2002: NRS 2002 is an evaluation system that comprehensively assesses a patient's nutritional status by disease status, recent weight loss of 5% or more, reduction in food intake, BMI, and age[32]. Patients with an overall score of 3 or more are considered to be at significant risk of malnutrition and need to undergo a detailed nutrition screening procedure immediately. If the score is less than 3, it is recommended to maintain the frequency of re-evaluation once a week during hospitalization[33]. The NRS 2002 scoring system is mainly used as a preliminary screening tool for nutritional risk, but it is not enough to directly identify malnutrition and its specific degree in patients[34]. In the application, the accuracy and effectiveness of the evaluation system may be further reduced if the patient's weight is not measured, or if the weight data is affected by fluid retention.

Malnutrition Universal Screening Tool: Based on the Malnutrition Universal Screening Tool (MUST) assessment system, key indicators such as a patient's BMI, unwanted weight loss, and presence of acute disease, the risk of malnutrition was divided into three levels: Low, medium, and high[35]. Studies have shown that in the nutritional status assessment of patients with colorectal cancer, MUST shows a high degree of consistency with the patient's subjective overall assessment

[36]. However, the applicability of MUST in the medical field of liver transplantation remains to be further explored.

Royal Free Hospital-Nutritional Prioritizing Tool: The Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) is used to assess the nutritional health of patients with cirrhosis in terms of BMI, involuntary weight loss, and daily dietary intake. Patients were further subdivided into three risk levels: Low, medium, and high[37]. In view of the phenomenon of fluid retention in patients with cirrhosis, which significantly improves the complexity of screening for malnutrition to a certain extent, RFH-NPT includes the factor of fluid retention, and compared with NRS 2002, RFH-NPT has a higher sensitivity[38]. Therefore, in 2019 European Society for Parenteral Nutrition selected it as the preferred tool for nutritional screening of patients with liver disease.

Dietary Inflammatory Index: The Dietary Inflammatory Index (DII)[39] is a novel nutritional assessment index that evaluates the potential anti-inflammatory or pro-inflammatory effects of diets by categorizing dietary components into 36 anti-inflammatory and 9 pro-inflammatory components based on the ability of the food and nutrients to affect serum levels of inflammatory markers. Duggan *et al*[40] showed that diets with high DII scores were associated with an increased risk of breast and other cancers in women, and another cross-sectional study showed that[41] high DII scores were positively associated with levels of relevant non-invasive liver markers such as alanine aminotransferase, aspartate aminotransferase, and liver injury. Cross-sectional study noted that diets with high DII scores were positively associated with levels of non-invasive liver markers such as alanine aminotransferase, aspartate aminotransferase, and the development of liver injury. Although DII has been shown to be strongly associated with the development of several inflammation-related diseases, its value in patients with hepatocellular carcinoma is unclear and needs to be further explored.

CLINICAL APPLICATION OF EARLY NUTRITIONAL INTERVENTION IN PATIENTS WITH LIVER CANCER AND LIVER TRANSPLANTATION

Influence of malnutrition on liver transplant patients

Although the specific role of malnutrition on the prognostic mechanism of liver transplantation has not been fully revealed, studies have shown that malnutrition can significantly increase the risk of complications and death of patients, and is a key factor affecting postoperative survival[42]. In addition, the presence of malnutrition and sarcopenia is closely related to the increase of infection and mortality after liver transplantation[43]. Meanwhile, in the study of Prakash *et al* [44], it was found that for recipients of living donor liver transplantation, the occurrence of malnutrition would increase the duration of postoperative mechanical ventilation and intensive care unit stay. Lee *et al*[45] also confirmed this view in their study, in which they emphasized that although there are multiple factors that may affect the clinical outcome of liver transplant patients, low vitamin D3 content is an independent risk factor. In addition, the liver after transplantation is unable to obtain sufficient glycogen support and effective glucose uptake, so the nutritional intake of patients not only needs to meet the urgent needs of metabolism, but also needs to provide the necessary energy reserve for the transplanted liver. Insufficient nutritional support, on the one hand, will lead to the decline of immune function, slow wound healing and muscle and respiratory function decline in patients, on the other hand, will further aggravate the risk of postoperative complications and increase the mortality[46].

Preoperative early nutritional support for liver transplantation patients

Before liver transplantation, the prevention of sustained loss of nutrition and muscle reserve is the main core goal of nutritional support, and vitamin and mineral deficiencies should be further corrected to minimize the risk of infection and debilitation of patients[47]. Early effective intervention against malnutrition can not only significantly prolong the survival period of patients, improve the quality of life, but also reduce the occurrence of postoperative complications to a certain extent, thus creating favorable conditions for liver transplantation. Nutritional support mainly includes enteral nutrition and parenteral nutrition. According to European Society for Parenteral Nutrition guidelines, enteral nutrition is recommended as the preferred nutritional support means, which is not only more consistent with the natural physiological mechanism of the human body, but also can significantly reduce the risk of complications by maintaining the complete structure and barrier function of the gastrointestinal mucosa[48]. Victor *et al*[49] found through literature analysis that early nutritional supplementation before the operation of liver transplantation patients can reduce the hospital stay of patients to a certain extent, and has certain clinical safety. In addition, Ramachandran *et al*[50] found that probiotic supplements can improve the nutritional status of patients to a certain extent and play an important role in reducing the severity of liver disease after giving probiotic intervention to patients with cirrhosis who received liver transplantation. At the same time, Sadanand *et al*[51] found through research observation that taking Lactobacillus plant-based before transplantation could reduce the occurrence of postoperative infection. However, results of larger studies are still needed to determine the specific mechanism of nutritional intervention.

Early postoperative nutritional support for liver transplantation patients

For patients after liver transplantation, the core of nutritional management is adequate protein and energy supply, so as to avoid excessive protein catabolism caused by surgery to the greatest extent[52]. The high metabolic status often associated with malnutrition was significantly associated with lower survival rates. In recent years, clinical practice has confirmed that adequate nutritional intake in the early stage after liver transplantation is not only conducive to post-

transplantation recovery, but also of great value in preventing post-transplantation complications[53]. Some specific nutrients that can play a complementary role in nutritional therapy after transplantation are called immune system modulators in clinic[54].

According to the study of Miyauchi *et al*[55], seven days before the ischemic injury of liver transplantation mice, after giving an enteral diet rich in antioxidant nutrients, adding vitamins C and E, and supplementing polyphenols, it was found that liver ischemia/reperfusion injury was significantly reduced, and antioxidant and inflammatory parameters could be improved to a certain extent, thus reducing liver cell injury. At the same time, Li *et al*[56] found in their study that in the early stage of liver transplantation, the recipient mice fed a supplemented tyrosine diet had longer survival time and reduced tissue damage. Moreover, in allograft liver transplantation, Pan *et al*[57] found that vitamin A could regulate gastrointestinal function after liver transplantation. In the study of Lindqvist *et al*[58], the nutritional regimen with a higher proportion of enteral nutrition and high-protein oral nutrition supplements in the early stage after liver transplantation would lead to increased protein intake of patients to a certain extent, but there was no significant difference between the two nutritional programs in postoperative severe outcomes. Although the current research on nutritional support for patients after liver transplantation due to biliary atresia, liver cancer, and non-alcoholic hepatitis is gradually in-depth, there is a relative lack of comprehensive nutritional management guidelines. Therefore, the indicators involved in this paper still need a large number of clinical studies to further improve.

THE MECHANISM OF EARLY NUTRITIONAL INTERVENTION IN LIVER TRANSPLANTATION FOR LIVER CANCER

In the human gut, there are complex microbial communities, including bacteria, fungi and archaea, which form a close mutually-beneficial symbiotic relationship with the human body. In a healthy state, the number and types of intestinal microbes remain constant, thereby jointly building the harmony of intestinal microecology. If this balance is broken, the imbalance of intestinal flora will be caused, which will not only lead to the disorder of intestinal function, but also affect the metabolism, cardiovascular, nervous and other systems of the human body, and then lead to a series of liver diseases [59].

Nutritional intervention and intestinal microecology

In recent years, studies have shown that nutrition intervention strategies have been proven to have significant effects on the regulation of human and animal intestinal microbial communities[60]. In this process, specific nutrients can not only act as an active participant in the energy supply or metabolic process, but also play a role in regulating the activity of the immune system, so it is considered as "immune nutrition". With the in-depth discovery of clinical studies, glutamine, arginine and probiotics are all key substances in immune nutrition[61]. Moreover, studies have revealed that the three components of ecological immune nutrition, probiotics, prebiotics and biostime, can directly act on the intestinal microecosystem[62]. At the same time, the study of Hussain *et al*[63] confirmed that the increase of dietary nutrients such as protein and fiber was related to the diversity and composition of duodenal microbiome. Meanwhile, recent studies have shown that immune nutrition plays a key role in maintaining intestinal function and health, especially in the aspect of intestinal mucosal barrier[64]. Therefore, the intervention of immune nutrients shows a strong protective and supportive effect at these three levels.

On the other hand, hepatocellular carcinoma, as a systemic inflammatory disease, the inflammatory response triggered by pro-inflammatory factors is important in its pathogenesis. The level of short-chain fatty acids (SCFA), which are metabolites of the intestinal microbiota, is closely related to the level of inflammation in the body, and butyrate (SCFA) can inhibit pro-inflammatory cytokines through inhibition of mediating the activity of histone deacetylase and binding to the G protein-coupled receptor (GPR), GPR41 and GPR43, in order to reduce inflammation[65]. It can be seen that the regulation of intestinal flora SCFA-producing bacteria to become the dominant strain is important in the suppression of body inflammation. Related studies have shown that dietary polyphenol-rich foods such as pomegranate, grapes, and broccoli are able to enrich butyrate-producing bacteria in a targeted manner, while diets high in dietary fiber are able to enrich SCFA-producing bacteria in a targeted manner[66]. Under a reasonable dietary structure, it is recommended to moderately increase the intake of anti-inflammatory dietary components and reduce the intake of pro-inflammatory dietary components, which is important in maintaining intestinal microbial homeostasis as well as suppressing the body's inflammatory response in tumor patients.

Mechanism of intestinal microecology in liver lesions and prognostic effects

In recent years, some scholars have observed significant changes in the structure and number of intestinal flora in patients with liver cancer, and this relationship between the gut and liver is called the "enterohepatic axis" (Figure 2). Yu and Schwabe[67] pointed out in their study that changes in intestinal flora are of great significance in determining the occurrence and development of hepatocellular carcinoma. Another study also confirmed significant changes in gut microbiota diversity in patients with liver cancer compared to healthy controls, and that porphyromonas and Bacteroides were associated with a reduced risk of liver cancer[68]. These findings reveal that the structural changes of intestinal flora in patients with early liver cancer can be used as a new marker for the diagnosis of early liver cancer to some extent, and its specific analysis is of great significance for the early warning of the disease.

In the progression of liver cancer, the imbalance of intestinal flora interacts with it, and with the deterioration of the disease, the imbalance of intestinal flora will be further aggravated. In an animal experiment exploring the interaction between intestinal microbiota and liver cancer, it was found that intestinal microbiota depletion can impair intestinal

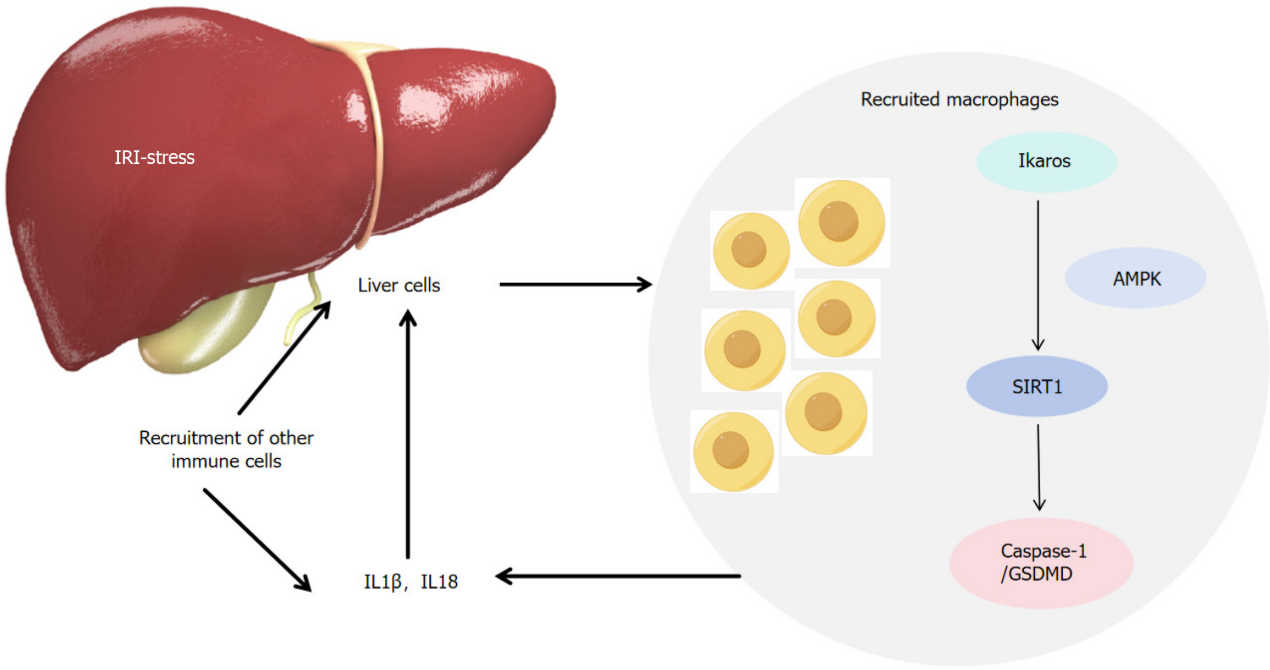

Figure 2 Gut-liver axis. The occurrence of ischemia reperfusion injury in the liver can trigger immune and inflammatory responses, resulting in the aggregation of neutrophils, macrophages and other immune cells at the injury site and the release of a large number of pro-inflammatory factors, thereby affecting the functions of the intestine and liver. AMP-activated protein kinase pathway plays an important regulatory role in this process. IRI: Ischemia/reperfusion injury; IL: Interleukin; AMPK: AMP-activated protein kinase; SIRT1: Sirtuin 1; GSDMD: Gasdermin-D.

tryptophan metabolism, thereby activating aromatics receptor, and thereby accelerate liver tumor genesis, and this process is related to up-regulation of sterol regulatory element-binding protein 2[69]. Feng *et al*[70] research team revealed that dysregulation of bile acid metabolism is related to the formation of cancer cachexia in mice. The experimental results showed that the intestinal flora of mice with hepatocellular carcinoma cachexia decreased in trichomillaceae and increased in enterobacteriaceae, and the microbial metabolism of bile acids decreased. Targeting bile acid metabolism with taurodeoxycholic acid and other drugs may contribute to the treatment of cancer cachexia. At the same time, studies have further confirmed that intestinal flora disturbance can lead to enterohepatic axis dysfunction by changing the bile acid metabolic pathway, thus promoting the occurrence and development of non-alcoholic fatty liver disease to a certain extent and accelerating its progression to cirrhosis and liver cancer[71].

In addition, the gut microbiota is an important modulator of the anti-tumor immune response in the liver. The body's innate immune system activates the adaptive immune system by detecting the gut microbiota and its metabolites to exert anti-tumor effects. Previous studies have pointed out that *Escherichia coli* strain Nissle 1917 has enhanced anti-tumor immune effects and can significantly enhance the inhibitory effects of transforming growth factor receptor blockers on tumor growth and metastasis[72].

Liver transplantation and intestinal flora

For patients with end-stage liver disease, liver transplantation is the primary way to prolong their lives. Although the results are remarkable, complications such as postoperative infection and rejection may endanger the function of the transplanted liver to some extent and seriously affect the postoperative survival of patients. Liver transplantation not only affects the ecological balance of the recipient's intestinal flora, but also causes significant changes in bacterial distribution and even causes abnormal bacterial migration[73]. At the same time, ischemia-reperfusion injury, immune rejection and antibiotic use during the operation together constitute the key factors for the imbalance of intestinal flora in the early stage after liver transplantation. Among them, ischemia-reperfusion injury is particularly critical, which not only weakens the integrity of intestinal mucosal barrier, promotes abnormal migration of intestinal bacteria, but also reduces intestinal immune function to a certain extent[74]. Bajaj *et al*[75] found that compared with homogenome, heterogenome showed a higher translocation rate of intestinal bacteria after transplantation, which was accompanied by a significant increase in endotoxin levels and aggravated liver function damage, further emphasizing the central role of immune mismatch in intestinal flora imbalance. Therefore, intestinal microbiography is also considered to be an important biomarker for predicting injury in liver transplantation[76]. At present, the prevention of intestinal flora imbalance and infection caused by bacterial displacement after liver transplantation has been widely studied. In a retrospective study, it was pointed out that the use of antibiotics before liver transplantation could destroy the microvilli of ileal epithelial cells, thus causing changes in the microflora, and thus effectively reducing liver transplant-related infections, thereby reducing liver injury and transplantation dysfunction[77]. At the same time, Jia *et al*[78] found that ciclosporin A could partially restore intestinal flora after liver transplantation and alleviate liver injury. However, further randomized controlled clinical trials are needed to elucidate the exact mechanism of action of these interventions, their target signaling pathways, and the optimal duration of treatment.

CONCLUSION

Status and challenges of early nutritional intervention in patients with liver cancer after liver transplantation

For liver transplantation patients with liver cancer, early postoperative nutritional intervention can effectively improve the prognosis of patients, and can reduce the incidence of postoperative infection and other complications to a certain extent. At the same time, changes in the patient's gut flora play an important role in this process. However, despite the great potential of early nutritional intervention, it still faces multiple challenges in practical application. The first is the individual differences in nutritional needs. Patients have different nutritional status and metabolic needs before and after surgery. Therefore, targeted nutritional support plans need to be formulated. Secondly, postoperative complications and drug therapy may affect patients' absorption and utilization of nutrients, and how to effectively maintain nutritional balance under these interfering factors is an important challenge. In addition, the collaboration of the healthcare team and the education of patients and families are also key factors in the successful implementation of nutrition interventions, and the lack of such support may affect the effectiveness of nutrition interventions.

Future research direction and development trend

Therefore, future research should aim to further explore strategies for individualized nutritional support and incorporate new nutritional drugs and treatments to optimize postoperative rehabilitation of liver transplant patients with liver cancer. In addition, interdisciplinary teamwork and the application of information technology may improve the efficiency and quality of nutritional support. With the advancement of science and technology and the increasing awareness of the importance of nutrition in disease management, it is expected that nutritional intervention will be more widely used and advanced in the field of liver transplantation for liver cancer in the future. The combination of these efforts will help to maximize the effect of postoperative nutritional interventions in liver transplant patients with liver cancer and improve the survival rate and quality of life of patients.

FOOTNOTES

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MINIREVIEWS

Advances in management strategies for enteral nutrition-related gastric retention in adult patients with nasogastric tubes

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Abstract

Gastric retention is a common complication in individuals receiving enteral nutrition (EN) *via* a nasogastric tube, increasing the risk of aspiration pneumonia and causing unnecessary interruptions in nutritional support. Given its clinical significance, establishing effective, evidence-based, and standardized management strategies is essential for bettering patient outcomes and mitigating complications. This review systematically synthesized the diagnostic criteria, assessment methods, influencing factors, management procedures, and intervention strategies for gastric retention in EN patients. Although no universal consensus exists regarding gastric residual volume (GRV) thresholds, evidence indicates that EN can continue at high GRV levels in the absence of gastrointestinal symptoms. Bedside ultrasound emerged as a non-invasive, and precise method GRV assessment, offering potential to standardize clinical practice. Key risk factors for gastric retention include neurological disorders and EN infusion rates exceeding 100 mL/h. Effective management strategies encompass non-pharmacological interventions, pharmacological agents, and traditional Chinese medicine (TCM) therapies. This review underscored the need for integrated, multi-modal management strategies and recommended the adoption of bedside ultrasound and standardized protocols to optimize EN delivery and improve patient outcomes. Large-scale, multicenter clinical trials should be a priority for future investigation to verify the effectiveness of TCM therapies and develop personalized intervention plans for high-risk patients.

Key Words: Enteral nutrition; Gastric retention; Management strategies; Gastric residual volume; Bedside ultrasound; General intervention; Pharmacological intervention; Traditional Chinese medicine

Core Tip: This study reviewed management strategies for gastric retention in adult enteral nutrition, emphasizing the need for standardized protocols. It highlighted bedside ultrasound as a novel gastric residual volume assessment method and advocated for a combination of non-pharmacological interventions, pharmacological treatments, and traditional Chinese medicine to improve patient outcomes. In addition, this review also called for further research and the implementation of personalized care plans.

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INTRODUCTION

Gastric retention refers to the accumulation of unemptied contents and volume in the stomach, leading to impaired nutrient absorption and an elevated risk of complications, including reflux and aspiration, significantly raising mortality rates of patients[1]. Generally, gastric retention poses a substantial clinical challenge for patients undergoing enteral nutrition (EN) by virtue of a nasogastric tube, as it often disrupts EN delivery, delays nutritional support, and heightens the risk of malnutrition and infection. Monitoring gastric residual volume (GRV) is an established and widely used strategy for assessing gastric emptying capacity and preventing reflux and aspiration pneumonia in EN patients[2]. While GRV monitoring is widely employed, its clinical application varies significantly, owing to the lack of consensus on the optimal GRV threshold and monitoring frequency. Surveys have revealed that nurses employ highly inconsistent GRV thresholds (ranging from 200 mL to 500 mL) to determine when to pause EN, reflecting the absence of a standardized approach in clinical practice[3,4]. Such inconsistency has contributed to unnecessary interruptions in EN, which negatively affect patient outcomes. For instance, Wang *et al*[5] observed that individuals with interrupted EN exhibited a threefold increase in malnutrition risk, a 30% higher probability of prolonged intensive care unit (ICU) stays, and a 50% higher risk of extended overall hospitalization. The outcomes above point to the pressing necessity of establishing refined, evidence-supported management protocols for gastric retention.

Current management strategies for gastric retention face several critical limitations. A major issue is the over-reliance on fixed GRV thresholds as the sole criterion for EN interruption, despite evidence indicating that GRV alone is a poor predictor of aspiration risk[6]. This practice often results in unnecessary EN suspensions, disrupting nutritional support and delaying patient recovery. Traditional GRV measurement using syringe aspiration is another limitation, as it is prone to procedural contamination, underestimation of gastric contents, and increased nursing workload[7]. Additionally, the variability in GRV monitoring intervals, with guidelines recommending assessments every 4 to 8 hours, creates inconsistencies in clinical practice and leads to fragmented patient care[8]. Addressing these limitations requires evidence-based protocols that incorporate multiple clinical indicators beyond GRV alone, as well as more efficient and standardized measurement methods.

This review addressed these gaps by proposing a novel, three-pronged management approach that integrated general interventions, pharmacological interventions, and traditional Chinese medicine (TCM) treatments into a comprehensive strategy for managing gastric retention. Unlike prior research focusing on isolated measures, this review highlighted the synergistic potential of combined approaches to optimize patient outcomes. It also promoted bedside ultrasound as a safer, more accurate alternative to syringe aspiration for GRV monitoring, addressing key limitations of current practice. By advancing evidence-based protocols that unified intervention strategies and measurement methods, this review aimed to minimize EN interruptions, optimize nutritional support, and promote patient recovery.

METHODOLOGY

Literature search

Studies published from 2000 to 2024 were systematically reviewed through an extensive search of PubMed, Embase, CNKI, and Web of Science databases. The search strategy included the following key terms: "gastric residual volume" OR "GRV" AND "enteral nutrition" OR "EN" AND "management" OR "intervention". Manual searches of citation lists from the selected studies were additionally executed to uncover related publications.

Study selection

We included literature that focused on adult patients receiving EN *via* a nasogastric tube and addressed management strategies for GRV. Studies involving pediatric patients or without directly addressing GRV management were excluded.

Data extraction

Data from included studies were narratively synthesized according to key themes and categorized into three main intervention types: Non-pharmacological, pharmacological, and TCM-based approaches. The synthesis focused on summarizing the effects of each strategy on GRV, EN continuity, and clinical outcomes.

Quality examination

The selected articles' methodological quality was appraised qualitatively rather than quantitatively, as this review aimed to provide a conceptual synthesis rather than a statistical meta-analysis.

OVERVIEW OF GASTRIC RETENTION

Diagnostic criteria

There is still no consensus among scholars, both domestically and internationally, on the diagnostic criteria for GRV in patients with EN[5,9,10]. The diagnostic criteria for gastric retention in China is that the GRV exceeds 200 mL or is greater than 50% of the infused volume[10-12]. High GRV is defined when GRV > 250 mL persists in two consecutive GRV measurements or when GRV surpasses 50% of the feeding amount administered in the prior 2 hours[13]. As indicated by Chinese guidelines[12], for intermittent nasogastric feeding, the GRV should be checked before each feeding, whereas for continuous nasogastric feeding, GRV should be assessed every 4-8 hours. Prokinetic agents can be used when gastric retention exceeds 250 mL; EN should be paused when GRV exceeds 500 mL, and the volume will be reassessed 4 hours later. The American Society for Parenteral and EN[8] suggested that EN should remain uninterrupted when GRV is under 500 mL. Moreover, routine GRV monitoring is not recommended for critically ill patients receiving EN unless patients experience symptoms of gastrointestinal intolerance, including diarrhea, abdominal distension, abdominal pain, or vomiting. As per the guidelines of the European Society for Clinical Nutrition and Metabolism[14], GRV monitoring is advised during the initiation and modification phases of EN, and EN is delayed if GRV exceeds 500 mL within 6 hours. The GRV between 250 mL and 500 mL, as recommended by the Canadian Critical Care Nutrition Guidelines[15], is acceptable in critically ill sufferers with EN, with GRV checked every 4 or 8 hours. A previous multicenter survey conducted in China[16] revealed that 150 mL (25.2%) and 200 mL (44.6%) were the most commonly applied GRV thresholds. The majority of nurses (84.3%) immediately suspend nasogastric feeding upon detecting high GRV. A systematic review[17] finds no significant correlation between GRV (200-500 mL) and aspiration or pneumonia, with a limited ability to predict aspiration-related pneumonia. However, such results may lead to unnecessary interruptions in nutritional supply. Therefore, EN is recommended to be maintained if GRV is below 500 mL, provided there are no other gastrointestinal intolerance symptoms. Some studies[17-19] have investigated less frequent GRV monitoring, demonstrating that it can decrease contamination risk, fluid exposure, and healthcare staff workload without increasing the incidence of complications. Based on the European Society for Clinical Nutrition and Metabolism guidelines[14] and domestic expert consensus[20], GRV should be monitored every 4 hours for individuals prone to aspiration or gastrointestinal intolerance. Additionally, literature has reported[21,22] that for high-risk aspiration patients, the methods of feeding should be transitioned to nasojejunal feeding, with parenteral nutrition provided as a supplement if GRV results in inadequate EN. Overall, there is still no consensus on GRV thresholds and the monitoring frequency across different regions. The phenomenon of artificial interruptions of EN in domestic settings is more pronounced. Relying solely on GRV thresholds to guide EN may be one-sided, and the guidance should be conducted on GRV thresholds combined with the gastrointestinal symptoms of patients.

Measurement methods

GRV monitoring provides dynamic insights into gastrointestinal motility and EN tolerance, and the volume of gastric contents can be measured and calculated using radionuclide imaging, aspiration, ultrasound, or Brix meter[5]. Radionuclide imaging is recognized as the gold standard for GRV measurement. Nevertheless, the high technical requirements and costs of this method render it unsuitable for routine bedside monitoring[20]. In contrast, bedside gastrointestinal ultrasound monitoring offers high accuracy for GRV assessment while maintaining the continuity of EN. Furthermore, this technique has emerged as a new technique in the implementation of EN due to its multiple advantages, such as ease of operation and non-invasiveness[23]. The gastric antrum is the optimal site for ultrasound monitoring, with ideal images achievable in 90%-100% of patients. Moreover, even when the residual volume is minimal, gastric contents can still be clearly observed[24]. Syringe aspiration is a widely applied non-invasive measurement technique due to its simplicity and time efficiency; however, it poses a risk of contaminating the nutritional formula[20]. Ohashi *et al*[25] discovered that aspiration, a non-standardized measurement method, was affected by various factors during practice, resulting in significant discrepancies between actual values and measured volumes. GRV monitoring may be influenced by multiple factors, such as the diameter of the nasogastric tube, syringe size, patient position, and operator's technique. Consequently, syringe aspiration may not accurately reflect the true GRV. Xiang *et al*[26] demonstrated no statistically significant difference ($P > 0.05$) between the bedside ultrasound method and the aspiration method by comparing these two methods in monitoring the feasibility and safety of GRV. However, the operation time for the bedside ultrasound method was markedly shorter than that for the aspiration method, with a statistically significant difference ($P < 0.01$). Bedside ultrasound can effectively assess GRV, shorten operation time, and reduce the workload of nurses. Despite this, syringe aspiration is the predominant method used by domestic nurses to measure GRV[16]. To optimize EN management and minimize interruptions caused by routine GRV monitoring, it is recommended to gradually transition

from syringe aspiration to gastric ultrasound as the preferred monitoring method.

MANAGEMENT STRATEGIES FOR PATIENTS WITH EN COMPLICATED WITH GASTRIC RETENTION

Identification and management of contributing factors

Jin[27] and Guo[28] identified several risk factors associated with gastric retention in critically ill patients receiving EN *via* nasogastric tubes. These factors include brainstem lesions, involvement of the autonomic nervous system, a history of mechanical ventilation and shock, Glasgow Coma Scale score < 8, mild hypothermia treatment, reduced bowel sounds, hypokalemia, hyponatremia, abnormal blood glucose, hypoproteinemia, and advanced age. Yu *et al*[29] monitored daily GRV in 63 critically ill patients with intracerebral hemorrhage undergoing EN. They observed a positive correlation between GRV and the Acute Physiology and Chronic Health Evaluation II scoring system ($P < 0.05$), along with a significant association between GRV and the Sequential Organ Failure Assessment score ($P < 0.01$). The trend in GRV changes can indirectly indicate the disease progression and prognosis of critically ill patients with intracerebral hemorrhage. The occurrence of gastric retention[21] has been reported to be correlated with the rate of EN infusion, with a remarkable increase in the risk of gastric retention when the infusion rate exceeds 100 mL/h. Feng *et al*[17] revealed that the appropriate nasogastric feeding volume and interval were crucial factors affecting gastric retention (Figure 1). The incidence of reflux and aspiration can be notably reduced through a single feeding volume of < 450 mL, an interval of approximately 5 hours, and maintaining a semi-recumbent position for at least 30 minutes after feeding. A meta-analysis [30] shows that intermittent nasogastric feeding using gravity or EN pumps for 30-60 minutes per session, 4-6 times per day, does not affect gastric retention, aspiration pneumonia, or nutritional outcomes compared to continuous nasogastric feeding. Cheng[31] tested the heater's clamping position across different speeds and investigated the temperature regulation of the EN solution at the outlet. A heating model, Y = 15.952 + 0.147X, was developed to ensure that the solution entering the body remains at 37°C, with Y indicating distance and X representing speed. A standardized EN heating system can effectively reduce the incidence of gastric retention. As revealed by a study[27], the incidence of gastric retention in neurocritically ill patients is time-dependent, peaking within the first week (68% of patients with gastric retention) and gradually decreasing thereafter. Additionally, gastric retention can still occur in the second and third weeks. Such results may be related to the body's intense stress response during the acute phase. Yu[32] developed a risk assessment model for gastric retention and conducted an evaluation. In this model, the risk levels were assigned based on the number of risk factors, with higher levels indicating a greater need for attention during the nursing process. Predictive care can then be provided according to the identified risk factors. Overall, the key factors affecting gastric retention include infusion rate, temperature, nasogastric feeding volume, and intervals. Given the ensuring daily caloric supply, adjustments can be implemented according to the sufferers' tolerance and response. Although the risk assessment model for gastric retention is still underdeveloped, further refinement and clinical application can enhance its ability to assess risks, guiding nurses in taking timely prevention and intervention measures.

Development of standardized procedures

An earlier study[33] suggested that 26% of EN interruptions could be avoidable. Reducing the frequency of EN interruptions and ensuring continuous, effective EN are key factors in improving the prognosis of critically ill sufferers with gastric retention. Chen and Wang[34] found that standardized management procedures for gastric retention could improve EN feeding target achievement rates and reduce prokinetic agent usage, while not notably affecting aspiration incidence. The specific procedures varied depending on GRV levels: (1) If GRV was < 200 mL, a 20 mL/h increment in infusion rate was applied, ensuring the rate did not exceed 120 mL/h; (2) If the GRV was between 200 mL and 350 mL, the original infusion rate was cut in half; (3) If the GRV ranged from 350 mL to 500 mL, the rate was decreased to 25% of the original speed; (4) When the GRV reached or exceeded 500 mL, the infusion was halted and the GRV was reassessed after 6 hours [referred to steps (1), (2), (3)]; (5) if the GRV was ≥ 500 mL and the Nutritional Risk Screening 2002 score was < 5, a switch to post-pyloric feeding was conducted; and (6) If the GRV was ≥ 500 mL and the Nutritional Risk Screening 2002 score was ≥ 5, 10 mg of metoclopramide (a prokinetic agent) was administered intramuscularly. Yang[35] recorded GRV and EN infusion rates using EN information management software, with notifications set at 6-hour intervals to remind nursing staff to monitor gastric retention. This software could automatically calculate the infusion rate and total volume, effectively reducing the number of EN interruptions due to gastric retention. Chen *et al*[36] improved the EN tolerance assessment form, incorporating factors such as abdominal distension, diarrhea, abdominal pain, nausea and vomiting, bowel sounds, gastric retention, aspiration, and drug contraindications as indicators of EN intolerance in critically ill individuals. Additionally, the corresponding grades and nursing measures were assigned, which contributed to standardizing and regulating the infusion rates of EN solutions and the use of prokinetic agents. As indicated by Jiang *et al*[37], GRV levels were categorized into various risk grades for gastric retention, and the corresponding operational procedures were systematically standardized with quantitative steps. Such procedures not only improved the feeding target achievement rates, but also effectively reduced GRV. Li *et al*[38] proposed the implementation of sequential EN intervention based on feedforward control in critically ill patients. This intervention began with the screening of high-risk patients, who were highlighted with red markers. Treatment was then carried out according to the assigned risk grades, allowing for the efficient allocation of nursing resources and reducing the occurrence of complications. In summary, the standardized nutrition support procedures have transformed passive management into proactive intervention, fully realizing standardized and regulated nursing. Additionally, these procedures have also enhanced overall enteral care to achieve effective dynamic interventions, thereby improving EN tolerance in patients.

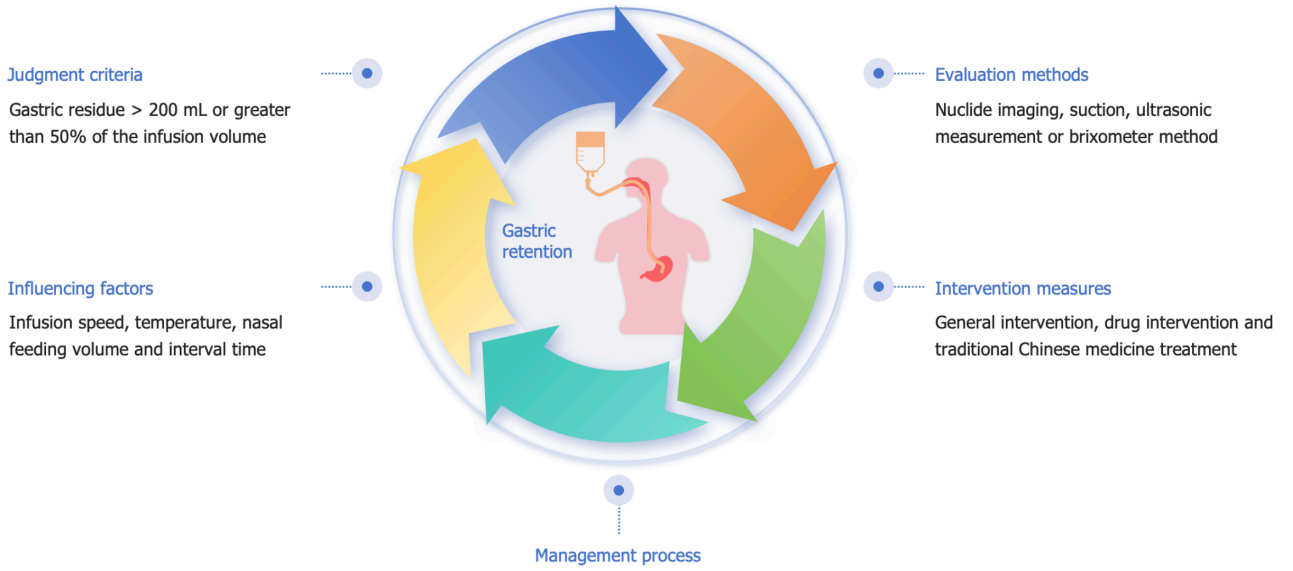

Figure 1 Assessment and intervention strategies for gastric retention in nasogastric feeding.

General interventions

Position management is a fundamental measure to prevent gastric retention in individuals suffering EN. A systematic review[39] revealed that maintaining a head-of-bed elevation of ≥ 30° during nasogastric feeding can lower the likelihood of gastric retention, reflux, aspiration, pneumonia and other complications, thereby improving the safety of EN. These outcomes matched the conclusions drawn in Hannah's study[4]. Liu *et al*[40] compared the relationship between three varying intervals (30 minutes, 60 minutes, and 90 minutes) of head-of-bed elevation (30°-45°) and GRV, indicating that maintaining a 60-minute elevation significantly promoted gastric digestion and emptying. Elevating the head of the bed to 40°-45° led to the highest safety of nasogastric feeding and the lowest risk of gastric retention. Yang *et al*[41] also recommended head-of-bed elevation to 45° in cluster nursing for preventing gastric retention in ICU patients. Additionally, semi-recumbent and right lateral positions were adopted alternately, along with abdominal massage. According to a previous article[42], abdominal massage can not only enhance vagus nerve activity, but also promote gastrointestinal motility. Furthermore, it can induce reflexive and mechanical effects on the gastrointestinal tract by altering intra-abdominal pressure, thereby promoting gastric emptying. Several systematic reviews[43,44] also confirmed that gastric retention in EN patients can be effectively minimized through abdominal massage. Hence, both position management and abdominal massage are safe, simple, and feasible interventions suitable for broad application in clinical practice. However, it should be noted that abdominal massage mainly targets the intestines, with the limited direct effect on the stomach. Further research and exploration in this area are warranted. Limb activities[28,41,45] have been illustrated to significantly promote gastrointestinal function and reduce gastric retention. These activities include passive movement, active movement in bed, position changes, and bedside activities. A study by Cao *et al*[45] explored the application of stage early upright mobilization in critically ill individuals. They found that the incidence of EN interruption due to increased GRV was markedly lower in the observation group than in the control group, demonstrating statistical significance ($P < 0.05$).

Pharmacological interventions

Erythromycin is known for its role as a macrolide antibiotic and motilin receptor agonist. It can strongly promote peristalsis in the stomach and proximal small intestine, induce significant antral contractions, and then accelerate gastric emptying. Apart from its prokinetic effects, erythromycin exhibits antibacterial properties, which may contribute to reducing the risk of gastrointestinal infections in certain cases[46]. Metoclopramide, a dopamine receptor antagonist, influences the chemoreceptor trigger zone centrally and gastric smooth muscle peripherally. Currently, the United States Food and Drug Administration has approved metoclopramide as the sole medication for treating gastric retention, with a recommendation for use limited to less than three months. A recommended dose of metoclopramide is 5-10 mg, administered three times daily[2]. Domperidone, a peripheral dopamine-2 receptor antagonist, can promote motility in the upper gastrointestinal tract, particularly the stomach. Moreover, it is effective in alleviating symptoms, such as vomiting and nausea[20].

TCM treatment

Various treatment methods exist in TCM for gastric retention, and their efficacy and mechanisms have gradually gained recognition[22]. Shan *et al*[47] stated that individuals with mechanical ventilation were treated with metoclopramide injection at bilateral Zusanli acupoints combined with abdominal massage. They discovered that the experimental group displayed a significantly lower incidence of gastric retention, abdominal distension, and vomiting than the controls ($P < 0.05$). Besides, a notable decrease was observed in the abdominal circumference after treatment. The above results confirmed the effectiveness of this combined method in reducing the incidence of gastric retention and related symptoms.

As indicated by Zhao and Tang[48], elderly patients with nasogastric feeding were treated with the Jianpi Tongwei Fang application at the Neiguan acupoint, followed by 5 minutes of moxibustion at the application site and an additional 5 minutes at the Zusanli acupoint. They demonstrated that the experimental group achieved superior efficacy in nasogastric feeding as against the control group, accompanied by a significant reduction in gastrointestinal reactions, including nausea, vomiting, and abdominal distension ($P < 0.05$). These results verified the effectiveness of integrating Chinese herbal medicine with moxibustion thermal stimulation applied to acupoints. Feng *et al*[49] followed the midnight-noon ebb-flow theory of TCM and performed massages on critically ill sufferers with EN based on the twelve meridians flow of Qi and blood. They uncovered that in comparison with the control group, the experimental group presented with considerably reduced gastric retention volume, increased feeding volume, and decreased incidence of aspiration pneumonia, with a notable difference in statistics ($P < 0.05$). Hu *et al*[50] applied auricular acupressure to ICU patients with EN, selecting a combination of five acupoints: Sympathetic, subcortex, brainstem, stomach, and spleen, guided by their clinical experience. Their results presented that the nutritional risk scores and GRV were evidently decreased in the experimental group, showing statistically notable differences ($P < 0.05$), inferring a positive effect on alleviating the symptoms of gastric retention and improving nutritional status. In the investigation led by Hu *et al*[51], elderly sufferers with gastric retention were treated with press needles combined with abdominal hot compresses (Figure 2). Stimulating specific acupoints combined with abdominal hot compresses can promote qi and blood circulation, alleviate spleen and stomach qi deficiency syndrome, and effectively enhance gastric emptying.

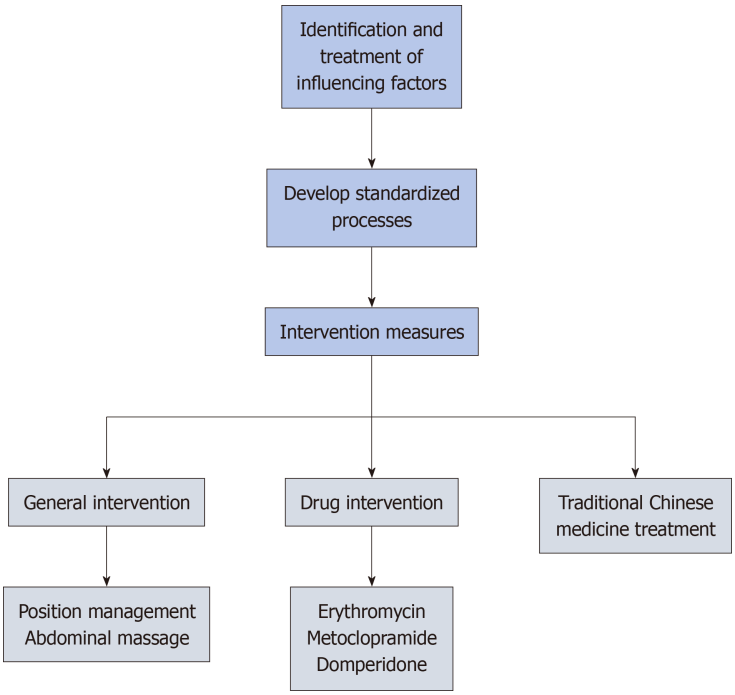

Figure 2 Multidimensional management of gastric retention in enteral nutrition.

Overall, TCM treatments have shown positive results in the treatment of gastric retention. However, most of the studies mentioned above involve small sample sizes, and lack detailed TCM syndrome differentiation and long-term follow-up data. Therefore, larger sample sizes and multicenter clinical studies required in the future to validate the efficiency and safety of TCM treatments, with the aim of promoting the standardization and normalization of TCM in treating gastric retention.

CONCLUSION

This study systematically reviewed and analyzed the literature on gastric retention in adult patients with EN by nasogastric tubes, comparing the thresholds and measurement methods used domestically and internationally. The findings highlight the importance of a comprehensive "three-pronged" management strategy that integrates non-pharmacological, pharmacological, and TCM-based interventions. This strategy addresses the limitations of single-intervention models, providing a patient-centered strategy to reduce EN interruptions, enhance nutritional support, and prevent complications such as aspiration pneumonia.

Our findings have significant clinical implications. Specifically, incorporating the "three-pronged" strategy into routine care can improve gastric retention management and reduce unnecessary EN interruptions. The adoption of bedside ultrasound for GRV monitoring is recommended as a safer, more efficient alternative to syringe aspiration. To support clinical translation, hospitals should acquire portable ultrasound devices, train healthcare staff on bedside ultrasound

procedures, and establish protocols for EN suspension and resumption. In addition, personalized care pathways should be developed to tailor interventions based on GRV thresholds and gastrointestinal symptoms, allowing for individualized treatment. Furthermore, strengthening post-discharge care is also essential to ensure patients and caregivers receive guidance on nutritional support and symptom monitoring, thereby reducing readmissions and promoting better long-term outcomes.

Despite recent progress in the management of gastric retention, numerous challenges remain. Future investigations should concentrate on large-scale, multicenter clinical trials to verify the effect and safety of different management strategies, promoting the standardization and normalization of gastric retention management. Additionally, the development of individualized treatment plans and comprehensive intervention measures is crucial for improving clinical outcomes and the quality of life of patients. Furthermore, post-discharge continuity of care should also be emphasized to provide more precise guidance for clinical practice.

FOOTNOTES

Author contributions: Feng LF and Jin LN conceptualized the study; Feng LF and Jin LN developed the methodology; Feng LF and Li XW conducted formal analysis; Feng LF and Zhu XQ curated the data; Feng LF drafted the original manuscript; Jin LN reviewed and edited the manuscript; Jin LN administered the project and acquired funding; Li XW contributed to the investigation; Jin LN supervised the study; Zhu XQ validated the results. All authors have read and approved the final manuscript.

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Abstract

Complete rectal prolapse, characterized by the protrusion of the rectal wall layers through the anal canal, poses significant treatment challenges, particularly due to controversies surrounding surgical approaches and the absence of a standardized assessment system. This study comprehensively reviews the main surgical techniques for complete rectal prolapse, categorized as transabdominal and transperineal/transanal procedures. Despite various techniques, challenges persist, including high recurrence rates and potential complications. Factors influencing the choice of the surgical approach include patient characteristics, symptomatology, and surgical expertise. With advances in medical technology, laparoscopic and robotic surgeries offer promising avenues, albeit with considerations of cost and accessibility. Ultimately, treatment plans tailored to the individual needs of the patient and surgical expertise are essential. Although controversies remain, the continued refinement of surgical techniques holds promise for improving outcomes in complete rectal prolapse surgery.

Key Words: Rectal prolapse; Surgery; Procedure; Treatment; Review

Core Tip: Selection of the appropriate surgical method depends on patient age, comorbidities, and prolapse severity when managing complete rectal prolapse. For high-risk patients, minimally invasive techniques like Delorme's or Thiersch's procedures offer quick recovery, but with a higher recurrence rate. In contrast, more invasive procedures like ventral mesh rectopexy provide durable results for severe cases. Postoperative follow-up is crucial to monitor for complications such as recurrence and bowel dysfunction. Tailoring the approach to individual patient characteristics is key to achieving the best outcomes and minimizing long-term complications.

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INTRODUCTION

Complete rectal prolapse, also known as external rectal prolapse, refers to the protrusion of the full-thickness rectal wall through the anal canal[1]. Although prolapse is most common among older women, it affects individuals of all ages, including children[2,3]. The causes of complete rectal prolapse are multifactorial, including genetic factors, anatomical structure, and increased intra-abdominal pressure. Currently, surgery is the only treatment modality offering a potential cure for rectal prolapse. The three primary goals of surgery for rectal prolapse: (1) To eliminate the prolapse by resecting or restoring normal anatomy; (2) To address associated functional abnormalities, such as constipation or fecal incontinence; and (3) To prevent the development of new gastrointestinal dysfunction[4]. Several surgical techniques have been developed to achieve these goals, each with its own advantages and disadvantages. The current assessment system for complete rectal prolapse requires improvement, and selecting an appropriate surgical approach remains controversial[5]. This study organizes and reviews the main surgical approaches for complete rectal prolapse, aiming to provide surgeons with a deeper understanding of these techniques and to collectively enhance the therapeutic outcomes for rectal prolapse.

DEFINITION AND CLINICAL PRESENTATION OF COMPLETE RECTAL PROLAPSE

Complete rectal prolapse refers to the downward displacement of part or all of the rectal wall, which protrudes completely from the anus. Rectal prolapse includes complete or incomplete, external or internal, and adult or juvenile prolapse. Rectal prolapse can occur at any age[6]. In adults, complete prolapse occurs when the entire rectal wall protrudes from the anus and is often accompanied by anatomical and functional abnormalities of the pelvic floor, such as rectocele, enterocele, and perineal descent. This condition may lead to symptoms such as mucosal or bloody stools, difficulty defecating, and anal incontinence[7].

SURGICAL APPROACHES FOR COMPLETE RECTAL PROLAPSE

Surgery is the treatment of choice for patients with a complete rectal prolapse. Numerous surgical options exist for the treatment of complete rectal prolapse, which are categorized into transabdominal and transperineal/transanal approaches based on the surgical technique.

Transabdominal rectal fixation

Transabdominal rectal direct suture fixation: Abdominal rectopexy involves fixing the rectal mesentery to the sacral promontory and has been reported to have a relatively high postoperative recurrence rate[8]. The key steps in the rectopexy procedure include cleansing the prolapsed rectal mucosa with cold saline solution, removing any foreign bodies and debris adhering to the mucosa, disinfecting the prolapsed rectal portion with a 0.1% potassium permanganate solution, applying iodine glycerin, gently reducing the prolapsed rectal portion manually, and plugging it with a rubber rectal plug. A vertical incision approximately 5-10 cm in length, is made in the lower left abdomen, and the abdominal cavity is opened. The assistant brings the prolapsed rectum forward from the anus to the vicinity of the abdominal incision, whereas the surgeon pulls the rectum into the abdominal cavity and fixes it to the left abdominal wall. Fixation requires the needle penetrating the serosa and muscle layers without piercing the mucosa. The rectum is fixed to the peritoneum and abdominal muscles (abdominal wall) using the two- to three-stitch knotting method. Subsequently, the peritoneum, muscle layers, and skin are sutured sequentially, and the abdominal incision is closed.

Transabdominal rectal patch fixation surgery: The ventral mesh rectopexy (VMR) procedure involves freeing only the anterior aspect of the rectum to the perineum, placing a patch at the lowest point of the anterior rectal wall, and suturing it in place[4]. The rectum is then suspended and fixed to the sacral promontory using a patch. VMR avoids posterior and lateral dissections of the rectum, reducing the risk of pelvic nerve injury[9]. The recurrence rate after VMR is comparable

to that after traditional suspension methods; however, VMR offers a higher rate of constipation relief, making it highly regarded. Currently, it is the preferred surgical procedure for rectal prolapse treatment among pelvic floor surgeons in Europe[10,11].

VMR rectopexy key points: At 1-2 cm above the umbilicus, a 1.2 cm incision is made to insert a trocar for insufflation, establishing a pneumoperitoneum at 11-13 mmHg. A 12 mm trocar is inserted at this site as the observation port, with the right McBurney's point serving as the primary operating port for the surgeon, and the intersection of the right external border of the rectus abdominis muscle with the line of the umbilicus as the secondary operating port. The intersection of the left external border of the rectus abdominis muscle with the line of the umbilicus serves as the primary operating port for the assistant, whereas the left reverse McBurney's point serves as the secondary operating port. After placing all ports, the patient is adjusted to a head-down, right-side position to explore the pelvis for any adhesions that may affect the surgery; if present, these adhesions must be separated first. The assistant raises the rectum with the left hand and pulls up the sigmoid mesocolon with the right hand to unfold the right sides of the rectum and sigmoid mesocolon, revealing a right-lateral rectal groove. The surgeon incised the peritoneum in the avascular area of the sacral promontory and then moves downward along the right lateral rectal groove to the lowest point of the Douglas pouch before turning to the left side. Attention should be paid to the sacral promontory to identify the right ureter and protect the inferior hypogastric nerve. In female patients, after incision at the lowest point of the Douglas pouch, the loose space between the rectum and vagina is located, and separation is carried out along this space until the lowest point of the rectovaginal septum is reached. In male patients, the posterior space of the prostate, known as the Denonvilliers' fascia, is entered after incising at the lowest point of the Douglas pouch. The Denonvilliers' fascia is then cut, entering the loose space between the Denonvilliers' fascia and the anterior rectal wall, known as the rectal anterior space. The assistant performs a digital rectal examination to confirm that the rectum is dissected to the lowest point, and once confirmed, a patch is placed. A biological patch (7 cm × 20 cm) is used, which induces minimal tissue reaction and has a lower risk of postoperative erosion. After securing the patch to the rectum, it is wrapped around its proximal end. With appropriate traction and tension, the position for patch fixation is estimated. Once determined, the assistant exposes the right sacral promontory. The proximal end of the patch is fixed to the sacral promontory using nonabsorbable sutures or hernia tacks. After securing the patch, the pelvic floor is sutured continuously with 3-0 barbed sutures, and the peritoneum is closed. Closing the pelvic floor peritoneum prevents adhesion or erosion of the patch to the small intestine, thereby preventing intestinal obstruction or perforation.

Transabdominal rectal posterior patch fixation (Wells rectopexy)

Wells rectopexy involves fixing the mesh to the posterior and lateral rectal walls. Short-term follow-up after surgery revealed recurrence rates ranging from 6% to 12%[12]. With prolonged follow-up, the recurrence rate increased[13]. Studies comparing the recurrence rates between VMR and Wells procedures reveal that VMR has a lower recurrence rate [12,14].

Laparoscopic Wells rectopexy key points: At 1-2 cm above the umbilicus, a 1.2 cm incision is made to insert a trocar for insufflation, establishing pneumoperitoneum at 11-13 mmHg. A 12 mm trocar is inserted at this site as the observation port, with the right McBurney's point serving as the primary operating port for the surgeon, and the intersection of the right external border of the rectus abdominis muscle with the line of the umbilicus as the secondary operating port. The intersection of the left external border of the rectus abdominis muscle with the line of the umbilicus serves as the primary operating port for the assistant, whereas the left reverse McBurney's point serves as the secondary operating port. After placing all ports, the patient is adjusted to a head-down, right-side position to explore the pelvis for any adhesions that may affect the surgery; if present, these adhesions must be separated first. The left colon is mobilized internally: The midline of the sigmoid mesocolon is incised; with intestinal forceps gripping the rectum and pulling it toward the abdomen, the sigmoid mesocolon is stretched, and the incision begins at the sacral promontory, following the "white-yellow junction" as a guide, cutting from the caudal to the cranial direction along the sigmoid mesocolon to the root of the mesentery. Then, turning left, a loose space is visible, entering the fusion fascial space between the left colonic mesentery and the anterior renal fascia (Toldt's space). Expanding Toldt's space: The assistant pulls the upper segment of the rectum toward the abdomen, the right-hand intestinal forceps grasp the root of the mesentery artery toward the cranial and ventral directions, maintaining tension, and the surgeon carefully expands Toldt's space: In this space, the surgical plane is expanded to the left to reach the Toldt line where the sigmoid mesocolon disappears. Care is taken to preserve the integrity of the left colonic mesentery and anterior renal fascia, leaving a transparent layer of the anterior renal fascia in front of the main iliac vessels. Through this fascia, the left ureter and genital vessels behind the root of the sigmoid mesocolon on the outer side can be seen (without damaging the inferior mesenteric plexus, left ureter, and left genital vessels). The dissection range extends from the center to the left, reaching the lateral gutter of the left colonic side, and from the caudal to the cranial side, reaching the root of the inferior mesenteric artery. The left colonic mesentery is mobilized externally, pulling the sigmoid mesocolon to the right, starting from the inherent adhesion band between the outer edge of the distal end of the sigmoid colon's first flexure and the left abdominal wall, the peritoneal reflection of the left colonic gutter is incised along the white-yellow junction (Toldt line) toward the cranial direction. The sigmoid colon is flipped to the right, and in the space between the mesentery and anterior renal fascia, known as Toldt's space, the left side is mobilized, ensuring protection of the left ureter and left genital vessels behind the anterior renal fascia. The left side of the sigmoid colon is completely opened to the midline and extended upward to the level of the lower sigmoid colon, ensuring the integrity of the anterior renal fascia, sigmoid mesocolon, and original descending mesocolon. Mobilization around the rectum: Starting from the sacral promontory level, in the loose connective tissue space behind the upper rectal mesentery, the surgical plane is expanded sharply to the posterior and lateral sides of the posterior rectal space until the gap between the rectal sphincter muscles is above. Posterior: Starting from the sacral promontory level and close to the

rectal mesentery, the surgical plane is expanded caudally in the posterior rectal space between the rectal mesentery and presacral fascia, cutting the rectosacral fascia, entering the gap of the levator ani muscle, and approaching the levator ani muscle. Laterally: The space around the rectum is expanded to both sides using the posterior gap as a guide, and the space around the rectum is mobilized to both sides until the level of the gap is above the levator ani muscle. Without cutting the inferior mesenteric or superior rectal arteries, detaching the lateral ligaments of the rectum, or opening the peritoneal reflection in front of the rectum, the integrity of the pelvic autonomous nerves is protected throughout the entire process. Posterior suspension fixation of the rectum A mesh patch is selected, trimmed to a suitable shape, and placed behind the rectum, ensuring that the patch is fully unfolded and spread flat in the gap behind the rectum. After the assistant raises the rectum and corrects the prolapse, the upper segment of the mesh is fixed to the anterior rectal fascia using absorbable sutures, the patch is buried, and careful hemostasis is performed. On the left side of the rectum, continuous sutures with 3-0 Vicryl suture are used to wrap and bury the left lateral peritoneum, mesh, and inherent fascia, avoiding contact between the mesh and the rectal surface and ensuring peritonealization of the left rectal side. The left outer layer of the sigmoid colon muscularis is sutured to the right lateral peritoneum, and the sigmoid colon is fixed on the lateral abdominal wall.

Transabdominal anterior patch fixation (Ripstein rectopexy)

Suturing the mesh around the anterior rectal wall in the Ripstein procedure leads to a high incidence of postoperative complications. McMahan modified the Ripstein procedure by fixing the ends of the mesh to the sides of the rectum rather than to the anterior rectal wall. The recurrence rate of McMahan's modified procedure is comparable to that of Ripstein surgery (2%-5%), with a complication rate of 20%[15]. The recurrence rate of rectal prolapse after Ripstein surgery and its modified procedures ranges from 4% to 10%[16]. Major postoperative complications are often related to the mesh, such as colorectal obstruction, mesh erosion into the intestine, ureteral injury or fibrosis, small bowel obstruction, rectovaginal fistula, and fecal impaction[17].

Laparoscopic Ripstein rectopexy key points: At a point 1-2 cm above the umbilicus, a 1.2 cm incision is made to insert a trocar for insufflation, establishing pneumoperitoneum at a pressure of 11-13 mmHg. A 12 mm trocar is inserted at this site as the observation port. At the same time, the right McBurney's point serves as the primary operating port. The intersection of the right external border of the rectus abdominis muscle with the line of the umbilicus serves as the secondary operating port for the surgeon. The intersection of the left external border of the rectus abdominis muscle with the line of the umbilicus serves as the primary operating port for the assistant, whereas the left reverse McBurney's point serves as the secondary operating port. After placing all ports, the patient is adjusted to a head-down, right-side position to explore the pelvis for any adhesions that may affect the surgery; if present, these adhesions must be separated first. Starting from the level of the sacral promontory, a sharp expansion of the surgical plane is performed posteriorly and laterally in the loose connective tissue space behind the upper rectal mesentery until it reached the space behind the rectum, up to the levator ani muscle space. Starting from the level of the sacral promontory, the surgical plane is expanded caudally in the posterior rectal space between the rectal mesentery and presacral fascia, cutting the rectosacral fascia, entering the space above the levator ani muscle and approaching the levator ani muscle. The space around the rectum is expanded on both sides using the posterior gap as a guide, the space around the rectum is mobilized on both sides until it reached the level of the space above the levator ani muscle. Without cutting the inferior mesenteric or superior rectal arteries, detaching the lateral ligaments of the rectum, or opening the peritoneal reflection in front of the rectum, the integrity of the pelvic autonomous nerves is protected throughout the entire process. Eventually, the posterior wall of the rectum is freed to the tip of the coccyx, raising the rectum. A 5 cm-wide mesh strap is placed around the upper rectum, and the mesh strap is fixed to the presacral fascia and periosteum under the sacral promontory using nonabsorbable sutures. The strap edges are sutured to the anterior and lateral walls of the rectum without repairing the pelvic floor. Finally, the peritoneum on both sides of the rectum is sutured, and the puncture holes are closed.

Transperineal rectal fixation

Transperineal resection for rectal prolapse (Mikulicz's procedure): Mikulicz's procedure can only remove the prolapsed portion of the rectum outside the anus and cannot address the underlying cause of the prolapse. Therefore, this surgery is only suitable for patients where the prolapsed rectum is severely swollen, adhered, cannot be reduced, or is already necrotic[18].

Mikulicz's procedure key points: In the lithotomy position, the buttocks are raised to prevent the intestines from falling into the rectovesical or rectouterine fossa and to avoid intraoperative injury. First, two traction sutures are placed at the distal end of the prolapsed bowel, and a circumferential incision is made 2 cm from the anal margin of the outer layer of the bowel wall. If the prolapsed bowel is long and the incision has penetrated the peritoneum, entering the prevesical or pre-rectal space and communicating with the abdominal cavity, only the gap between the inner and outer bowel layers is incised without entering the abdominal cavity. After cutting the bowel wall, bleeding points are ligated. The seromuscular layers of the inner and outer bowels are intermittently sutured with fine silk thread (for short prolapsed bowels, only muscular layer suturing is performed), and the abdominal cavity is closed. To avoid contamination of the abdominal cavity, a small portion of the outer bowel wall can be cut open during suturing, and the abdominal cavity can be closed promptly. Using the same method, the seromuscular (or muscular) layer of the posterior wall of the bowel is sutured after the inner and outer bowel layers. By cutting and suturing simultaneously, the anterior half of the inner layer of the bowel is gradually cut off, and the inner and outer layers are sutured with 2-0 or 3-0 chromium-plated intestinal threads. This suture layer is placed at the distal end of the first layer. Using the same method, the full-thickness posterior wall is cut and sutured, the prolapsed bowel is removed, and the bowel is gradually inserted into the anus with fingers to complete the surgery. A piece of gauze is placed in the rectum with a 1 cm rectal tube inside and then bandaged with a sterile dressing.

Transanal rectal mucosal sleeve resection with muscular folding sutures (Delorme's procedure): The Delorme procedure, a classic perineal procedure, was previously less commonly used because of its higher recurrence rate. However, it has gained increasing attention in recent years due to its simplicity, minimal invasiveness, and low requirement for patient surgical tolerance[19]. It is primarily suitable for older adult patients at high risk for anesthesia, pediatric patients with primary rectal prolapse, and young men concerned about potential nerve damage[20,21]. The Delorme procedure is suitable for older adult patients with a prolapsed rectal length of less than 5 cm[22]. However, studies have reported good efficacy in patients with a prolapse length of 5-10 cm[23,24]. The Delorme procedure is a viable option for repeat surgery [19,25].

Delorme's procedure key points: After a successful epidural or general anesthesia, the patient is placed in the lithotomy position. At the 1, 3, 6, 9, and 11 o'clock positions, #7 silk sutures are used to suture and tract the perianal skin, thereby exposing the surgical field. Oval forceps are used to grasp the rectum, gradually pulling outward to expose as much of the intestine as possible. Silk suture #7 is placed at the 1, 3, 5, 7, 9, and 11 o'clock positions along the site of the lithotomy incision to suture the top of the prolapsed intestinal tube mucosa and serve as traction lines to pull the prolapsed rectum. At the point where the intestinal mucosa protrudes 1.5-2 cm below the dentate line, a circular mark is made using an electric knife. An electric knife is used to cut along the marked line to open the mucosal layer of the prolapsed intestine, sharply dissecting upward along the submucosal layer and exposing the rectal muscle. Circular dissection is performed to determine the length of the freed rectal mucosal tube based on the degree of rectal prolapse, which usually ranges from 6 to 15 cm above the dentate line. The rectal mucosal tube is incised at the 6 and 12 o'clock positions of the lithotomy site. A vertical folding suture of the rectal circular muscle is performed using 3-0 absorbable suture material to strengthen the pelvic floor muscle function. The rectal mucosa is severed, and closure is performed using 3-0 absorbable sutures.

Transperineal rectosigmoidectomy (Altemeie's procedure): Altemeie's procedure is characterized by its minimal trauma, quick recovery, and low incidence of complications[26,27]. Moreover, it has a minimal impact on sexual function and can be repeated in cases of recurrence. Its main indications include full-thickness rectal prolapse, typically with a prolapse length greater than 5 cm; rectal prolapse with incarceration; older adult and frail patients who cannot tolerate abdominal surgery; middle-aged and young patients who are unwilling to undergo abdominal procedures; and young men[28-30].

Altemeie's procedure key points: The patient is placed in the lithotomy position under either spinal or general anesthesia. Sutures are placed at the 2, 4, 8, 10, and 12 o'clock positions around the anus to provide traction, open the anal canal, and allow the rectum to protrude externally. The dentate line is exposed, and a mark is made using an electrocautery device that measured approximately 1.5-2.5 cm from the dentate line as a cutting margin. The outer layer of the rectum is incised along this mark, followed by sequential layer-by-layer incisions down to the muscular layer. Care is taken during this step to avoid damaging the inner layer of the rectum. The rectal mesentery is dissected from the bowel, and the pelvic peritoneum is opened and flipped back to reduce the prolapsed rectum. Further dissection separates the inner rectal mesentery and part of the sigmoid colon, with careful ligation of the blood vessels to prevent bleeding. The upper pelvic peritoneum is sutured to the rectum or anterior wall of the colon to reconstruct the pelvic floor. After confirming the cutting line, the bowel is transected, and the cut ends are anastomosed end-to-end using absorbable sutures. A drainage tube is placed in the rectum and removed three days later if no abnormalities are observed. The wounds are inspected for signs of significant bleeding and dressed to complete the procedure.

Perineal stapled prolapse resection procedure: Perineal stapled prolapse resection (PSPR) procedure Scherer *et al*[31] performed the PSPR procedure for the first time in 2008 using a stapler to excise the excessively prolapsed rectum. Currently, it is recommended for older adult and frail patients who cannot tolerate abdominal surgery and have mild intestinal edema[32]. The PSPR surgery is characterized by its simplicity, short operation time, quick postoperative recovery, and minimal complications[33,34].

PSPR procedure key points: Before surgery, bowel preparation is performed, and the patient is placed in the lithotomy position under general anesthesia. Adequate exposure is ensured, and tissue forceps are used to pull out the prolapsed intestinal segment fully, confirming that no other organs are involved between the prolapsed intestinal walls. A linear cutting stapler is used to open the prolapsed intestine at the 12 o'clock position with an incision approximately 1 cm above the dentate line. Similarly, the opposite side (6 o'clock) of the prolapsed intestine is opened to separate the prolapsed rectum, resembling a French window. The separated intestinal segments are transected approximately 1 cm below the dentate line. Absorbable sutures are used to completely suture the anastomotic sites (1, 2, 4, 5, 7, 8, 10, and 11 o'clock positions) for reinforcement and hemostasis.

Anal austerity surgery (Thiersch's operation): Thiersch operation strengthens the tension of the external anal sphincter, which is suitable for patients where the anal sphincter lacks contraction or has become lax due to rectal prolapse[35]. It is often used as an adjunct or transitional procedure to other surgeries[36,37]. Moreover, it can be used for the treatment of anal incontinence[38].

Thiersch operation key points: The procedure is performed under epidural or spinal anesthesia with the patient in the lithotomy position. A semicircular incision is made from the 3 to 9 o'clock positions at the upper margin of the anus, approximately 1 cm above the anal margin (white line), to reach the superficial component of the external anal sphincter for hemostasis and ligation. The upper edge of the incision is gradually dissected at the level of the dentate line. Tissue forceps grasp the upper edge flap at the 6 o'clock position and push it inward to convert the semicircular incision into a longitudinal incision. Excess skin corners are trimmed, and the muscle layer, mucosa, and skin are vertically sutured in layers. The tightness of the sutures allows the anus to stretch and accommodate two fingers under anesthesia.

DISCUSSION

Complete rectal prolapse can severely affect the quality of life of patients[11]. Statistical data showed that the incidence of complete rectal prolapse in the population is 0.5%, with women being approximately six times more likely to be affected than men[4]. The etiology of complete rectal prolapse is complex, and currently accepted theories include the sliding hernia theory, rectal intussusception theory, pudendal nerve injury theory, and theories involving pelvic floor tissue laxity and anal sphincter weakness[39]. The most common symptoms of complete rectal prolapse include protrusion, mucus secretion, bleeding, increased bowel movements, and a feeling of incomplete evacuation. It is often accompanied by constipation or fecal incontinence, and severe cases may lead to acute complications such as incarceration and necrotic rectal prolapse[40]. The diagnosis of complete rectal prolapse primarily relies on objective examination, and in emergencies, the possibility of an underlying malignancy should be considered[41].

Surgery remains the primary treatment for complete rectal prolapse[42]. The ideal surgical approach should correct these abnormalities, prevent prolapse, restore normal bowel function, and address fecal incontinence while alleviating constipation[43]. Table 1 summarizes the indications, advantages, and disadvantages of different surgical approaches. The perineal approach is recommended for older adult or frail patients to avoid general anesthesia and laparotomy, whereas abdominal approaches have gained popularity in recent years owing to their lower recurrence rates[44]. However, studies comparing the Altemeier and Delorme procedures have not observed significant differences in recurrence rates or postoperative complications[45]. Another multicenter randomized controlled trial comparing four surgical methods (Delorme, Altemeier, sutured rectopexy, and resection rectopexy) did not observe significant differences in the recurrence rates or complications[46]. Studies have suggested that the recurrence rate of perineal approaches is ten times higher than that of abdominal approaches[47]. Research has observed that in female patients with complete rectal prolapse, the incidence of complications is lower with the Altemeier procedure, which can improve bowel movements in constipated patients[48]. Meta analysis suggests that treatment of rectal prolapse in male patients undergoing abdominal procedures was associated with longer operative times, lower recurrence rates, and similar complications to perineal procedures[49]. Studies have shown that compared to laparoscopic suture rectopexy, laparoscopic mesh rectopexy is associated with a lower recurrence rate of rectal prolapse but a longer operative time[50]. These findings indicate that different surgical methods have widely varying outcomes in different individuals, and the optimal surgical approach for treating complete rectal prolapse remains elusive[51,52]. Postoperative care following rectal prolapse surgery plays an important role in the patient's perioperative recovery. Key components of postoperative care include dietary guidance, wound management, and appropriate physical activity. By providing scientific and effective guidance during the recovery period, the occurrence of complications can be minimized, and the patient's postoperative rehabilitation can be accelerated.

The therapeutic outcomes of surgery for complete rectal prolapse are unsatisfactory, primarily because of high recurrence rates. According to relevant data, the recurrence rate after surgical treatment can reach 10%-20% or even higher[53]. Additionally, surgical treatment may lead to complications, such as fecal incontinence and anal stenosis, thereby affecting the quality of life. How to further improve surgical efficacy, restore normal bowel function, reduce recurrence rates, and minimize complications remains a matter of concern[54]. Many factors influence the choice of surgical approach and method for complete rectal prolapse, including subjective factors such as regional customs, the expertise of specialized physicians, and the difficulty of the surgery, as well as objective factors such as the extent of rectal prolapse, the baseline conditions of the patient, assessment of anal function, sex, recurrence rates, intraoperative and/or postoperative complications, patient acceptance, and economic considerations[55-57]. The choice of the surgical method for patients with complete rectal prolapse primarily depends on the clinical characteristics of the patient and the experience of the surgeon. Currently, relevant treatment guidelines are available to assist surgeons in selecting the most appropriate surgical approach[10]. According to the guidelines, preoperative evaluation should include an assessment of anatomical defects, causes, degree, and symptoms of prolapse; consideration of comorbidities; evaluation of anal function; and the overall condition of the patient to determine the suitability for surgery and the optimal approach and specific surgical method[58].

With continuous advancements in medical technology, surgical methods for complete rectal prolapse are evolving. Currently, surgical approaches for complete rectal prolapse mainly involve laparoscopic and robotic surgeries. Laparoscopic surgery, characterized by minimal trauma, rapid recovery, and reliable efficacy, has become one of the main methods for complete rectal prolapse surgery[5,59]. El-Dhuwaib *et al*[60] analyzed the epidemiological trends of rectal prolapse surgery in the United Kingdom from 2001 to 2012 and observed that the popularity of laparoscopic rectopexy increased sharply. Compared with other rectal prolapse surgeries, this procedure showed better results in terms of hospital stay, mortality, and reoperation rates[60]. Robotic surgery is a novel surgical method developed in recent years, characterized by precise operation and smaller incisions; however, it is costly and has not yet been widely adopted[61,62].

This study reviews the main surgical methods for treating complete rectal prolapse and their key operative points to provide surgeons with a reference for selecting surgical approaches. By considering the basic condition of the patient and surgical indications, selecting surgical methods that meet the needs of the patient and the expertise of the surgeon, and advocating for minimally invasive and individualized treatment, personalized treatment plans can be developed, steering clinical treatment strategies for complete rectal prolapse toward individualization and customization.

CONCLUSION

In conclusion, the choice of surgical method for complete rectal prolapse remains controversial, and treatment outcomes

Table 1 Summary of surgery for complete rectal prolapse

Surgical types	Surgical methods	Indications for surgery	Advantages	Disadvantages	Outcomes	Complications
Transabdominal rectal suture fixation	Transabdominal rectal suture fixation	Suitable for patients with complete rectal prolapse, no major comorbidities	Simple, effective in preventing prolapse recurrence	Higher complication rate, more invasive than other techniques	High success rate, effective in preventing recurrence. Recurrence rate 23.33%	Infection, bleeding, bowel injury, prolonged recovery
Transabdominal rectal patch fixation surgery	Ventral mesh rectopexy	Indicated for patients with rectal prolapse and multiple pelvic organs prolapse	Reduced recurrence rate, good outcomes in most cases	Risk of mesh-related complications, longer recovery time	Effective for complex cases, low recurrence. Recurrence rate 4%	Mesh infection, bowel injury, bowel obstruction, recurrence
	Wells rectopexy	Indicated for patients with extensive prolapse and poor pelvic support	Good for severe prolapse, restores rectal function	High complication risk, more invasive	Effective in severe prolapse cases, high recurrence rate. Recurrence rate 6% to 12%	Infection, bleeding, bowel injury, mesh-related complications
	Ripstein rectopexy	Suitable for patients with extensive anterior rectal prolapse	Effective for anterior prolapse, durable results	Longer operation, higher complication rate	High success rate, especially for anterior prolapse. Recurrence rate 2% to 5%	Bowel injury, recurrence, constipation, prolonged recovery
Transperineal rectal fixation	Mikulicz's procedure	Recommended for elderly or high-risk patients	Minimal surgical trauma, quick recovery	Risk of prolapse recurrence, lower long-term success	Effective in short-term, high recurrence rate	Bleeding, infection, recurrence, incontinence
	Delorme's procedure	Suitable for elderly, frail patients with non-complex prolapse	Minimally invasive, good for elderly patients	High recurrence rate, requires careful technique	High short-term success rate, but risk of recurrence	Rectal injury, bleeding, infection, incontinence, anastomotic stenosis and dehiscence
	Altemeie's procedure	Ideal for patients with significant rectal prolapse and bowel dysfunction	Reduces prolapse, restores function	Risk of complications, more invasive compared to other perineal approaches	Effective in long-term management, reduces recurrence. Recurrence rate 0% to 29%	Infection, bowel injury, anastomotic leak, incontinence
	PSPR procedure	Suitable for patients with moderate prolapse who are poor surgical candidates	Minimally invasive, quicker recovery, low complication rate	Higher risk of recurrence compared to abdominal procedures	Effective in treating prolapse with good short-term results. Recurrence rate 12%	Staple line breakdown, recurrence, bleeding
	Thiersch's operation	Best for patients with recurrent prolapse who are poor surgical candidates	Simple, low-risk procedure	Higher recurrence rate, limited applicability	High recurrence rate, not as effective for complex prolapse cases	Subcutaneous infection, anal stenosis

PSPR: Perineal stapled prolapse resection.

are still not entirely satisfactory. However, with the continuous advancement in medical technology, the direction for development of complete rectal prolapse surgery has gradually become clearer. With the continuous improvement and refinement of surgical techniques, the efficacy of complete rectal prolapse surgery will continue to improve in the near future.

FOOTNOTES

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MINIREVIEWS

Neoadjuvant therapy: Dawn of reducing the high post-surgery recurrence rate of hepatocellular carcinoma

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Abstract

The high postoperative recurrence rate remains a major challenge in the treatment of hepatocellular carcinoma (HCC) following resection. Increasing research has been delved into investigating the role of neoadjuvant therapy on the prognosis of resectable HCC. Recent trends in combination therapy with molecularly targeted agents and immune checkpoint inhibitors have significantly improved the efficacy of systemic antitumor treatments, yielding survival benefits exceeding 40%. Neoadjuvant therapy for HCC, whether based on systemic antitumor treatments, locoregional therapies, or their combination, has emerged as a promising research direction. However, there remains a matter of debate on neoadjuvant therapy. In this review, we summarize and discuss the research progress and challenges of neoadjuvant therapy for HCC over the past five years from the perspective of Chinese guidelines to provide new insights and future directions in this field.

Key Words: Hepatocellular carcinoma; Neoadjuvant therapy; Locoregional therapy; Molecularly targeted drug; Immune checkpoint inhibitor

Core Tip: Currently, numerous articles focus on preoperative antitumor therapy for hepatocellular carcinoma (HCC). Of note, this review uniquely examines neoadjuvant therapy for HCC within the context of combination therapy from the perspective of the China Liver Cancer Stage. Drawing on the Chinese guidelines, it addresses the definition of the neoadjuvant therapy concept, identifies the target population, evaluates the outcomes of various treatment strategies, and discusses the challenges regarding neoadjuvant therapy for HCC.

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INTRODUCTION

Primary liver cancer has long been a significant burden on global healthcare, affecting the Western Pacific region, including China, in a disproportionate manner, with approximately 80% of cases being hepatocellular carcinoma (HCC) [1]. The latest data from the World Health Organization indicate that up to 71% of new cases of HCC worldwide are in the Western Pacific region, with 42% of cases in China[2]. Despite surgical resection of the tumor, the 5-year postoperative recurrence rate is still as high as 40%-70%. These findings indicate that HCC is a highly recurrent disease with a poor prognosis[3].

In China, a country with a high incidence of HCC, guidelines for the diagnosis and treatment of HCC emphasize a more aggressive surgical strategy, focusing on the extent of the tumor burden. Hepatic resection for patients with Barcelona Clinic Liver Cancer stage (BCLC) B/C HCC with normal liver function, large isolated tumors, multinodular tumors, macrovascular invasion, or portal hypertension is considered to have a higher long-term survival rate than other nonsurgical treatment modalities. The key to enhancing the prognosis of patients with HCC is to reduce the elevated recurrence rate observed in patients following surgical intervention. This has become a central focus for researchers globally, including those in China.

Consequently, the investigation of neoadjuvant therapy aimed at reducing the incidence of postoperative recurrence is gaining special interest within the field of clinical research. With the combination of molecularly targeted drugs and immune checkpoint inhibitor (ICI) treatment becoming mainstream, neoadjuvant therapy has great potential advantages. Nonetheless, neoadjuvant strategies are still controversial in many aspects, such as patient selection, timing of interventions, and efficacy of therapy. Currently, there is no uniform standard for neoadjuvant therapy for HCC, and issues such as personalized regimens still need to be further explored.

This review offers a comprehensive and systematic overview of HCC neoadjuvant therapy, encompassing key issues such as the conceptualization of the treatment, the population for which it is indicated, neoadjuvant therapy studies in HCC published in the last five years, the current challenges of the therapy and ongoing clinical studies.

THE CONCEPT OF NEOADJUVANT THERAPY AND TARGET POPULATION

Neoadjuvant therapy first emerged in the 1980s[4,5]. Since then, the concept of neoadjuvant therapy and related concepts have undergone continuous improvement. Concurrently, related concepts in the treatment of HCC have also evolved. According to the most recent Chinese guideline for diagnosis and treatment of primary liver cancer (2024 edition), neoadjuvant therapy is defined as the preoperative treatment of patients who are eligible for surgical resection but have high-risk factors for postoperative recurrence[6,7]. Thus, studies on HCC that are not candidates for surgical resection, and studies on antitumor therapy prior to other radical treatments such as ablation and liver transplantation, are excluded.

The independent risk factors of neoadjuvant therapy include the number and size of the tumor the number and size of the tumor, microvascular invasion (MVI), invasive biological characteristics (such as preoperative alpha-fetoprotein level), the severity of chronic liver disease, and surgery-related factors. In accordance with the criteria set forth by the China Liver Cancer Stage (CNLC), surgical resection is a viable option for all stages, from Ia to IIIa[6]. Nevertheless, there is no evidence that patients with stage Ia disease can benefit from neoadjuvant therapy[8]. Furthermore, they may also forfeit the opportunity for surgical intervention due to adverse effects or insensitivity to neoadjuvant therapy; therefore, neoadjuvant therapy is not recommended for patients with stage Ia disease. Furthermore, patients with HCC presenting with CNLC IIb/IIIa have a high tumor load and poor biological behavior compared with patients with early-stage HCC. It is therefore recommended that neo-adjuvant therapy should be carried out with caution following a multidisciplinary discussion and consent process (Figure 1).

Overall, the overarching objective of neoadjuvant therapy is to facilitate curative transformation in patients, thereby extending their long-term survival prospects. Neoadjuvant therapy is recommended for patients with CNLC Ib/IIa and selected IIb/IIIa HCC that are suitable for surgical resection.

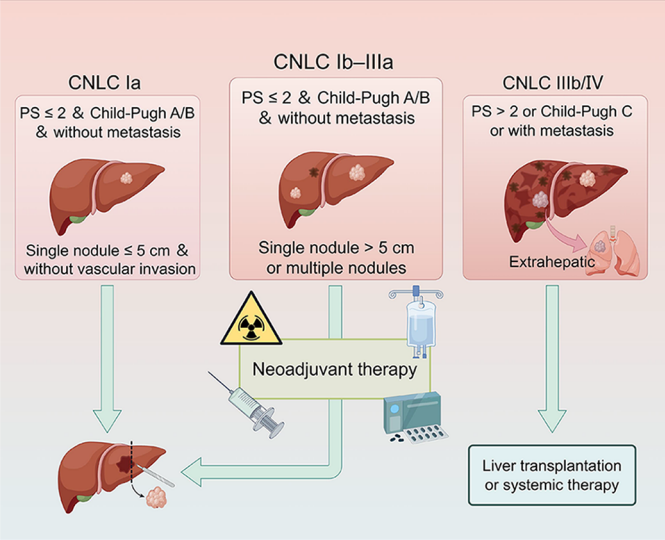

Figure 1 Hepatocellular carcinoma patients recommended for neoadjuvant therapy in the Chinese guideline for diagnosis and treatment of hepatocellular carcinoma (2024 edition). CNLC: China Liver Cancer Stage; PS: Performance status. Created by figdraw.com (Supplementary material).

RESEARCH PROGRAMS FOR NEOADJUVANT THERAPY IN THE LAST FIVE YEARS

Locoregional therapy in neoadjuvant therapy

Interventional therapy: Transcatheter arterial chemoembolization (TACE) represents the earliest explored avenue of neoadjuvant therapy for HCC and is currently the most commonly utilized interventional therapy for HCC. In recent years, the clinical value of neoadjuvant TACE has become evident, largely owing to advances in technology, including superselective embolization and drug-loaded microsphere embolization (Table 1)[9,10].

Fang *et al*[11] conducted a randomized controlled trial of 164 patients with BCLC stage A/B disease beyond the Milan criteria. The overall survival (OS) and progression-free survival (PFS) rates were significantly higher in the neoadjuvant TACE group than in the hepatectomy-only group (HR: 0.3602; 95%CI: 0.1914-0.6779; P = 0.0011). This trial also showed the safety of neoadjuvant TACE therapy since no considerably increased incidence of serious adverse events. Furthermore, a European multicenter retrospective study was conducted to explore the efficacy of neoadjuvant TACE therapy in patients with resectable HCC larger than 5 cm[12]. Compared with the pre-resection group, the neoadjuvant TACE group did not significantly differ in terms of disease-free survival (DFS; HR: 1.017; 95%CI: 0.676-1.530; P = 0.935) or OS (HR: 0.670; 95%CI: 0.373-1.202; P = 0.172). Remarkably, further subgroup analyses revealed TACE improved OS only in patients with HCC larger than 0 cm (HR: 0.258; 95%CI: 0.061-1.093; P = 0.045), whereas it was identified as a critically significant factor in patients with portal vein tumor thrombus (PVTT; HR: 0.523; 95%CI: 0.245-1.118; P = 0.087) and single giant HCC (HR: 0.478; 95%CI: 0.221-1.030; P = 0.052). Japanese scholars have also reached similar conclusions regarding neoadjuvant therapy for resectable HCCs larger than 5 cm[13]. Additionally, a meta-analysis of five studies, including 1556 patients with HCC larger than 5 cm, also indicates that the long-term survival impact of neoadjuvant TACE is contingent upon the specific chemotherapy regimen employed[14]. Compared with single-agent chemotherapy, the combination of chemotherapeutic agents was associated with superior outcomes in terms of OS and DFS. However, the impact on intraoperative bleeding was found to be limited.

In addition to TACE, hepatic arterial infusion chemotherapy (HAIC) is also employed as a neoadjuvant interventional therapy for HCC. Neoadjuvant TACE can result in a severe inflammatory response called postembolization syndrome, which may increase the risk of bleeding in the context of subsequent surgical procedures[15]. In contrast, HAIC avoids this limitation by eschewing embolic agents and producing a lesser degree of inflammatory response.

A team of researchers from Sun Yat-sen University investigated a study to investigate the survival benefit of neoadjuvant HAIC in patients with resectable HCC and PVTT[16]. The OS rates at 5 years (OR: 0.88; 95%CI: 0.47-1.65) and recurrence-free survival (RFS) rates at 5 years (OR: 0.75; 95%CI: 0.28-1.98) were greater in the neoadjuvant HAIC group than in the surgical group. Furthermore, the combination of HAIC and TACE has been demonstrated to increase survival in patients[17]. These data suggested that TACE in conjunction with HAIC therapy is associated with a higher conversion rate and improved PFS in patients with initially unresectable HCC. Additionally, the incidence of grade 3/4 adverse events appeared to be comparable between the two groups. Therefore, TACE-HAIC may be regarded as a more efficacious alternative, paving the way for neoadjuvant interventions.

Taken together, the use of neoadjuvant interventions is more beneficial in patients with larger tumors and high-risk recurrence factors, such as PVTT, who are selected for such therapy. The promotion of refined therapy concepts, such as super-selective embolization, has broadened the scope for benefit among patients undergoing neoadjuvant therapy. Notably, the use of intervention as a standalone neoadjuvant therapy is not a common practice, both domestically and internationally.

Table 1 Summary of neoadjuvant locoregional therapy studies in hepatocellular carcinoma in the last five years

Disease	HCC stage/liver function	Treatment arms (*n*)	Neoadjuvant duration (weeks)	Preoperative stopping time (weeks)	Median follow-up (months)	Primary endpoints findings	Ref.
Resectable HCC	BCLC A/B exceeding the Milan criteria	Neoadjuvant TACE (82) *vs* direct surgery (82)	4-6	NA	36	1-year OS (97.2% *vs* 82.4%); 2-year OS (88.4% *vs* 60.4%); 3-year OS (71.6% *vs* 45.7%; $P = 0.0011$)	Fang *et al* [11]
Resectable HCC (> 5 cm)	NA	Neoadjuvant TACE (60) *vs* direct surgery (324)	NA	NA	24	DFS ($P = 0.935$); OS ($P = 0.172$)	Giannone *et al*[12]
Resectable HCC (> 5 cm)	Child-Pugh A/B	Neoadjuvant TACE (30) *vs* Direct surgery (30)	12	NA	24	2-year DFS ($P = 0.7045$)	Kobayashi *et al*[13]
Resectable HCC with PVTT	Child-Pugh A	Neoadjuvant HAIC (65) *vs* direct surgery (55)	9.6	NA	36	1-year OS (94.9% *vs* 84.6%); 3-year OS (78% *vs* 47.6%); 5-year OS (66.4% *vs* 37.2%; $P < 0.001$)	Hu *et al*[16]
Centrally located resectable HCC	Child-Pugh A	Neoadjuvant IMRT (41) *vs* direct surgery (121)	5-6	4-12	45	1-year OS (95% *vs* 82%); 3-year OS (70% *vs* 64%); 5-year OS (70% *vs* 54%; $P = 0.0099$); 1-year DFS (71% *vs* 52%); 3-year DFS (53% *vs* 38%); 5-year DFS (37% *vs* 34%; $P = 0.034$)	Wei *et al* [19]
A single and small (≤ 5 cm) HBV-related resectable HCC	BCLC A	Neoadjuvant IMRT (30) *vs* direct surgery (30)	NA	4	68	DFS ($P = 0.448$)	Salem *et al* [20]

TACE: Transcatheter arterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy; IMRT: Intensity modulated radiotherapy; HCC: Hepatocellular carcinoma; PVTT: Portal vein tumor thrombus; BCLC: Barcelona Clinic Liver Cancer; OS: Overall survival; DFS: Disease-free survival; NA: Not available.

Radiotherapy: Neoadjuvant radiotherapy may reduce postoperative recurrence rates and improve postoperative survival (Table 1).

A retrospective study conducted at Peking Union Medical College Hospital examined the long-term survival rates of patients with central HCC who underwent neoadjuvant radiotherapy[18]. The findings of the present study indicated that, in comparison with surgical resection alone, there was a notable distinction in OS (HR: 0.47; 95%CI: 0.24-0.93; $P = 0.0099$) and DFS (HR: 0.56; 95%CI: 0.34-0.92; $P = 0.034$) between the neoadjuvant radiotherapy group and the surgical group alone. Another researcher investigated patients with hepatitis B virus-associated small HCC who were at high risk of MVI[19]. The presence of MVI had a significant effect on the survival outcomes of these patients. However, neoadjuvant intensity-modulated radiotherapy has a favorable response rate and minimal toxicity.

Furthermore, internal radiation therapy has the potential to be a valuable addition to HCC therapy as a neoadjuvant radiotherapy option. It is believed to be a viable alternative to TACE in terms of efficacy and safety[20]. Nevertheless, it has not been employed on a significant scale for the treatment of HCC patients in China, largely because of the elevated cost and the paucity of data pertaining to HCC patients in China.

The advent of sophisticated technologies such as 3D conformal radiotherapy and intensity-modulated radiotherapy has enabled the delivery of higher doses of radiation with greater precision to the target area. This has led to an increased tumor response rate and a reduction in the incidence of therapy-related side effects. It is therefore evident that precision radiotherapy represents a key area of ongoing development.

Systemic antitumor treatment in neoadjuvant therapy

Systemic antitumor treatment represents a significant treatment modality for patients with HCC at all stages of disease progression. This approach primarily encompasses the use of molecular targeted drugs and ICI treatment. Particularly the "T-A regimen" (atezolizumab plus bevacizumab), which received approval in 2020, has represented a significant advancement in the field of systemic antitumor treatment for HCC[21]. Subsequent regimens, including sintilimab plus a bevacizumab biosimilar and camrelizumab plus rivoceranib, have demonstrated comparable efficacy[22,23]. At present, this combination therapy is gaining recognition as a standard approach. Another significant advancement in immune drugs was the success of the dual immune combination regimen of tremelimumab plus durvalumab (STRIDE regimen) in 2022. This finding was subsequently validated in further studies in Asian subgroups[24,25]. Nevertheless, the utilization of systemic antitumor treatment in the neoadjuvant therapy of HCC remains an area of ongoing investigation (Table 2).

Table 2 Summary of neoadjuvant systemic antitumor treatment studies in hepatocellular carcinoma in the last five years

Disease	HCC stage/liver function	Treatment arms (*n*)	Neoadjuvant duration (weeks)	Preoperative stopping time (weeks)	Median follow-up (months)	Primary endpoints findings	Ref.
Resectable HCC	AJCC stage Ib, II, and IIIb	Neoadjuvant cemiplimab (21)	6	4	NA	Significant tumor necrosis: 20% (4/20)	Marron *et al*[26]
Locally advanced resectable HCC	Child-Pugh A	Neoadjuvant cabozantinib + nivolumab (15)	8	4	12	AEs: 93.3% (14/15)	Ho *et al* [27]
Resectable HCC	CNLC IIb/IIIa	Neoadjuvant camrel-izumab + apatinib (18)	6	7	12	MPR: 17.6% (3/18); pCR: 5.9% (1/18)	Xia *et al* [28]
Resectable HCC	Child-Pugh A	Neoadjuvant nivolumab + ipilimumab (14) *vs* nivolumab (13)	6	NA	24.6	Grade 3 AEs: 43% (6/14) *vs* 23% (3/13)	Kaseb *et al*[29]

HCC: Hepatocellular carcinoma; AJCC: American Joint Committee on Cancer; CNLC: China Liver Cancer Stage; AEs: Adverse events; MPR: Major pathological response; NA: Not available.

A single-arm phase II study was conducted to evaluate the efficacy of cemiplimab in patients with neoadjuvant HCC [26]. With the exception of one patient in whom lymph node metastasis was identified intraoperatively and the procedure was therefore aborted, the remaining 20 patients underwent successful surgical resection under the guidance of an external medicine specialist. The disease control rate (DCR) was 100%, with an objective response rate (ORR) of 35%. However, the long-term efficacy of this treatment has not been disclosed because of the limited follow-up period. The feasibility of cabozantinib in combination with nivolumab was evaluated in a study of neoadjuvant therapy for borderline or locally advanced HCC[27]. A major pathological response (MPR) was achieved in 33.33% (5/15) of the patients, and no significant adverse events were observed in any of the patients. This highlights the initial instance of molecularly targeted drugs being employed in conjunction with ICI treatment in the context of neoadjuvant therapy for HCC. The team led by Academician Xue-Hao Wang conducted a phase II clinical study of perioperative treatment with camrelizumab plus rivoceranib[28]. The results demonstrated an ORR of 33.33% (6/18) and a 1-year PFS rate of 53.85% (95%CI: 24.77-75.99%). During the neoadjuvant therapy phase, 16.7% (3/18) of patients reported adverse events of grade 3/4, indicating that the regimen was safe and manageable. Furthermore, the article emphasizes the necessity of postoperative adjuvant therapy to increase the low pathological response rates associated with low-intensity neoadjuvant therapy. The results of a subsequent phase II clinical trial of dual-immunity combination therapy, the nivolumab plus ipilimumab regimen for the perioperative treatment of HCC, demonstrated that the median PFS in the dual-immunity combination group was 19.53 months [95%CI: 2.33-not estimable (NE)], whereas it was 9.4 months (95%CI: 1.47-NE) in the immunological monotreatment group[29]. Additionally, 33% (95%CI: 7.5%-70.1%) of patients in the combination therapy group achieved an MPR. In the combination therapy group, adverse effects were observed, yet overall safety and tolerability were maintained. Concurrently, many neoadjuvant systemic antitumor treatment studies are currently in progress[30-32].

In summary, in current systemic antitumor treatments for HCC, molecularly targeted drugs or ICIs have limited efficacy and are easily tolerated; thus, combination therapy has become mainstream. However, further studies including neoadjuvant therapy with larger samples and longer follow-up periods are needed.

Combined locoregional and systemic antitumor treatment in neoadjuvant therapy

As both local therapies (vascular intervention, radiotherapy) and systemic antitumor therapies (molecular targeted drug treatment, ICI treatment) have their own therapeutic advantages and different antitumor mechanisms, attempting to combine therapeutic approaches to explore potential synergistic effects to improve patient survival is currently an important trend in the treatment of HCC (Table 3).

Radiotherapy has previously been considered to have the advantages of altering the HCC tumor microenvironment and facilitating the synergistic effect of systemic antitumor agents[33]. In a phase Ib clinical trial, 20 patients with BCLC stage 0-A HCC received neoadjuvant therapy with stereotactic body radiotherapy combined with tislelizumab[34]. The ORR was 63.2%, and the DCR was 100%. There were no surgical delays in any of the patients, and there was no increase in surgical difficulty or complications. During neoadjuvant therapy, no grade 4/5 adverse events occurred in any patients. In 2023, Zhu *et al*[35] reported a study of neoadjuvant therapy in 20 cases of resectable HCC with TACE in combination with camrelizumab/sintilimab. The ORR and DCR in the neoadjuvant group were 75.0% and 100.0%, respectively, with 70.0% of patients successfully downstaged. However, the study revealed a limited survival benefit in the neoadjuvant group compared with the surgery-only group ($P > 0.05$). In contrast, another protocol involving neoadjuvant TACE and tislelizumab monoclonal antibodies for the treatment of resectable or critically resectable HCC showed a significant survival benefit[36]. Patients receiving neoadjuvant therapy had significantly better PFS ($P = 0.041$) and OS ($P = 0.006$) than those receiving surgery alone. The incidence of MVI in the neoadjuvant group was 4.9%, whereas it was greater than 60% in the surgery-alone group. There was only one grade 3/4 event (elevated ghrelin transaminase). A study by Wu *et al*[37] with HCC treated with neoadjuvant TACE combination with lenvatinib and ICIs (sintilimab/

Table 3 Summary of neoadjuvant locoregional combined with systemic antitumor treatment studies in hepatocellular carcinoma in the last five years

Disease	HCC stage/liver function	Treatment arms (*n*)	Neoadjuvant duration (weeks)	Preoperative stopping time (weeks)	Median follow-up (months)	Primary endpoints findings	Ref.
Resectable HCC	BCLC 0-A/CNLC I	Neoadjuvant tislelizumab + SBRT (20)	4	4	60	Delay of surgery: 0; AEs: 100%; Grade 3 AEs: 40% (8/20); Grade 4 or 5 AEs: 0; ORR: 63.2% (12/19); DCR: 100%; pCR: 10.5% (2/19)	Li *et al* [34]
Resectable HCC	CNLC II	Neoadjuvant TACE + ICIs (20)	8-22	4	24	ORR: 75.0% (15/20); DCR: 100.0%; 1-year DFS: 86.6%; 1-year OS: 100.0%; 2-year OS: 76.4%	Zhu *et al*[35]
Resectable or borderline Resectable HCC	CNLC Ib/IIa/IIIa	Neoadjuvant TACE + tislelizumab (41) *vs* direct surgery (41)	6	4	24	AEs: 87.8% (36/41); pCR: 31.7% (13/41); MPR: 43.9% (18/41); incidence of MVI: 4.9%	Zhao *et al*[36]
Resectable HCC	CNLC Ib-IIIa	Neoadjuvant lenvatinib + ICIs + TACE (24) *vs* direct surgery (76)	9	3	24	1-year OS (100% *vs* 92.1%); 2-year OS (100% *vs* 48.7%; P = 0.003)	Wu *et al* [37]
Resectable HCC with Cheng's type I/II PVTT	Child-Pugh A	Neoadjuvant TKIs + ICIs + TACE (33) *vs* direct surgery (105)	6	4	60	1-year RFS (75.0% *vs* 55.0%); 3-year RFS (61.3% *vs* 22.7%); 5-year RFS (61.3% *vs* 19.9%; P = 0.002)	Hou *et al*[38]
Resectable HCC with macrovascular invasion	CNLC IIIa	Neoadjuvant TKIs + ICIs + TACE/HAIC/RT (22) *vs* direct surgery (40)	16	4	24	RFS (P = 0.046)	Wu *et al* [39]

TACE: Transcatheter arterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy; SBRT: Stereotactic body radiotherapy; HCC: Hepatocellular carcinoma; PVTT: Portal vein tumor thrombus; BCLC: Barcelona Clinic Liver Cancer; CNLC: China Liver Cancer Staging; OS: Overall survival; AEs: Adverse events; DFS: Disease-free survival; ORR: Objective response rate; MPR: Major pathological response; pCR: Pathological complete response; RFS: Recurrence free survival; DCR: Disease control rate; MVI: Microvascular invasion; TKIs: Tyrosine kinase inhibitors; ICIs: Immune checkpoint inhibitors; RT: Radiotherapy.

camrelizumab/tislelizumab/pembrolizumab/toripalimab) also supported previous observations. In the neoadjuvant group with the triplet regimen of TACE combined with lenvatinib and ICI, 83.3% of patients achieved an objective response and had significantly longer DFS (P = 0.019) and OS (P = 0.003) than did the surgery-alone group. Another study supporting the survival benefit perspective included 138 patients with resectable HCC with type I/II PVTT treated with a similar regimen and reported that 78.8% of patients achieved an objective response, and neoadjuvant therapy was an independent protective factor for OS (HR: 0.433; 95%CI: 0.195-0.964; P = 0.040) and RFS (HR: 0.458; 95%CI: 0.233-0.897; P = 0.023)[38].

One study focused on the postoperative safety of combined neoadjuvant regimens[39]. A total of 20 multicenter patients receiving different regimens of combined local, targeted drug, and ICI neoadjuvant therapy for HCC were included. The study concluded that neoadjuvant therapy markedly decreased the hazard of tumor recurrence (HR: 0.39; 95%CI: 0.15-0.98; P = 0.046), and in patients with HCC with macrovascular invasion, combined neoadjuvant therapy significantly reduces the rate of tumor recurrence (P = 0.018) and maintains a relatively safe profile in the postoperative period. However, this therapy can also cause chronic liver injury and increase the risk of nontumor-related death (P = 0.036). Therefore, combined neoadjuvant local and systemic antitumor treatment reduces tumor recurrence and achieves survival benefits with overall safety and control.

Some of the ongoing clinical trials are promising. A trial of cadonilimab, the world's first clinical-stage PD-1/CTLA-4 bispecific antibody, in combination with HAIC for neoadjuvant therapy of patients with resectable CNLC Ib/IIa HCC is ongoing[40]. Two other clinical trials of local combined systemic antitumor neoadjuvant therapy from Sichuan University Huaxi Hospital and Tsinghua Changgeng Hospital are also ongoing, and the results of these trials are expected to be published gradually in the future[41,42].

CURRENT CHALLENGES OF NEOADJUVANT THERAPY

Effects on surgery

Neoadjuvant therapy may produce an inflammatory response in the tissue, increasing the probability of tissue fibrosis, which in turn has an impact on the difficulty of maneuvering during surgery. One study revealed that cancer-associated fibroblasts significantly remodel during neoadjuvant therapy, differentiating into new cell subtypes, which may increase the complexity of surgical resection[43]. It has been suggested that significant tissue fibrosis/inflammation may occur within the tumor tissue after neoadjuvant therapy, which may affect the anatomy at the time of surgery and make tumor resection more difficult[44]. However, it has also been suggested that even though intraoperative adhesions are more severe in patients after neoadjuvant therapy, they do not affect the surgical operation, and instead, the median time of surgery can be shortened owing to tumor downstaging[45]. Thus, at this point in time, there is still a lack of conclusive evidence on the impact of neoadjuvant therapy on the difficulty of performing intraoperative operations due to tissue fibrosis, and most of the studies did not analyze in detail the intraoperative challenges faced by the surgeon; thus, there is still some controversy on this issue.

Another effect of neoadjuvant therapy on surgical maneuvers is bleeding. Some molecularly targeted drugs inhibit tumor neovascularization by blocking the VEGF pathway[46]. This blocking effect not only affects the tumor vasculature but also may affect the generation and proliferation of normal vascular endothelial cells, leading to decreased vascular renewal and thus increasing the risk of bleeding. For example, anti-angiogenic targeted drugs such as bevacizumab may lead to increased liver texture fragility, thereby increasing intraoperative bleeding and surgical difficulty. This type of bleeding differs from mucosal bleeding in that its incidence is closely related to the anatomical location of the tumor, the type of histopathology, and the different drugs or doses used[47]. This calls for the surgeon to assess the patient's risk of bleeding carefully before performing the procedure take appropriate preventive measures and choose the right time for intervention. The intraoperative use of new materials is also an option worth considering[48].

Careful timing of interventions

As part of the perioperative treatment, neoadjuvant therapy plays only an auxiliary role, and the core is still subsequent surgery. If the emphasis on neoadjuvant therapy leads to significant delays or even delays in surgery, making HCC patients who could have received surgical resection lose the opportunity for surgery, this is not worth the loss. Therefore, controlling the timing of therapeutic interventions is particularly important. Several important timing points are of great concern. When to start neoadjuvant therapeutic intervention, when to end neoadjuvant therapeutic intervention, and when to perform surgery are all therapeutic interventions whose timing needs to be carefully chosen. With respect to the timing of neoadjuvant therapy, it is generally believed that neoadjuvant therapy should be initiated as soon as possible after the patient is admitted to the hospital and relevant examinations should be completed to avoid delaying the disease. In terms of the length of the neoadjuvant therapy cycle, according to the current consensus of neoadjuvant experts and related studies, the neoadjuvant therapy cycle should usually be given for 6-12 weeks, with a maximum of 16 weeks. The key is not to rely on imaging changes but rather to operate as soon as possible after the therapeutic goal is achieved[8]. Moreover, the timing of drug withdrawal needs to be carefully considered because of concerns about tumor progression and surgical safety. A short withdrawal period increases intraoperative and postoperative risks; a long withdrawal period increases the likelihood of postoperative recurrence. Currently, the minimum recommended discontinuation time is 4 weeks after the last TACE treatment, 2-4 weeks for ICIs, 1 week for small molecule targeted drugs, and 4-6 weeks for bevacizumab monoclonal antibodies to avoid the risk of intraoperative bleeding[7,8].

In future studies, the length of treatment time from the first neoadjuvant therapeutic intervention to the final intervention in HCC patients, the time from admission to surgery in HCC patients, and the time from the final neoadjuvant therapeutic intervention to discontinuation of the drug for surgical resection in HCC patients are worthy of focus as indicators of outcome.

Security concerns

Patients receiving neoadjuvant therapy may experience a decline in physical status, including treatment-related adverse events and increased perioperative liver function. In particular, with the current trend toward combination treatment regimens, the increased intensity of treatment may lead to improved outcomes but is also associated with an increased risk of perioperative complications. Previous studies evaluating TACE combined with targeted and ICI treatment in intermediate to advanced HCC patients compared with TACE alone or TACE targeted alone combined with ICI treatment have shown an increase in adverse events and an acceptable safety profile[49,50]. This emphasizes the complex balance between relevant efficacy and potential complications and the need for broader studies by expanding sample sizes, as well as targeted studies in neoadjuvant therapy.

In clinical practice, it should be noted that both local therapy, systemic antitumor therapy, and a combination of the two have unique advantages and limitations. Different treatments have different characteristics and cutting-edge changes. Standardized and accurate therapeutic decisions should be based on guidelines and high-level evidence-based medical evidence, as well as on the latest advances and research findings in each field. However, a single clinical department may have limitations and lags in other areas of therapeutic approaches, whether in terms of medication experience, timing of treatment, or updating of cutting-edge knowledge. Therefore, another effective initiative to reduce the adverse events and perioperative risks associated with neoadjuvant therapy is to conduct multidisciplinary treatment [51,52]. The communication and cooperation between multidisciplinary teams should be strengthened to ensure appropriate and individualized treatment decisions for patients, and timely assessment and intervention of adverse events are important measures to improve the safety of neoadjuvant therapy and even its efficacy in HCC patients.

Unpredictable efficacy

HCC, a highly heterogeneous malignancy, is resistant to treatment and causes headaches for many physicians[53,54]. Current neoadjuvant treatment regimens, regardless of their type, suffer from limited tumor response rates. Therefore, although the numerous neoadjuvant therapy study protocols vary and there are differences in the setting of study endpoints, the focus on and assessment of treatment response, such as objective remission rates, remains at the core of each study.

Postoperative efficacy is even more difficult to predict, and prognosis-related biomarkers seem to be important options. One study explored the significance of the platelet-lymphocyte ratio in radiotherapy[55]. Platelet-to-lymphocyte ratio (PLR) was found to be correlated with basic tumor characteristics, multiple oncologic factors, treatment outcomes, and toxicity. A high PLR was mostly associated with poor clinical features and prognosis. Similar observations were made in another study on the relevance of the neutrophil-to-lymphocyte ratio to patient survival after lenvatinib treatment[56]. The level of serum alpha-fetoprotein, a classical tumor marker, is still of great value in predicting, among other things, OS and the recurrence rate after resection[57]. Some emerging biomarkers are also popular for research. For example, one study reported that serum CXCL9 and LAG-3 levels were correlated with treatment efficacy and may be markers for predicting the response to the "T-A regimen"[58]. However, large sample studies on combination therapy and specific studies on neoadjuvant therapy are lacking. Moreover, some biomarkers are not routinely measured in clinical practice, and their monitoring may increase the difficulty of testing and the cost to the patient; thus, there is a need to emphasize more readily available biomarkers to increase clinical tractability. In addition, modeling predictive assessment is a promising line of research.

Thus, selecting appropriate study endpoints and identifying reliable biomarkers to predict the response to and prognosis of patients receiving neoadjuvant therapy are essential for guiding regimen selection, optimizing the timing of interventions, and assessing surgical prognosis in patients with HCC.

ONGOING CLINICAL STUDIES

We searched ClinicalTrials.gov for registered clinical trials and screened 43 clinical trials for neoadjuvant treatment of HCC under the CNLC concept (Supplementary Table 1). We found rich applications of neoadjuvant regimens, especially various combination regimens, including the combination of molecularly targeted agents with ICIs, the combination of "the dual immune combination regimen", and the combination of local therapy with systemic antitumor therapy. It is encouraging that the control group in some studies was also expanded from the previous surgery-only group to the neoadjuvant therapy group without a combination regimen. This means not only the importance and safety of neoadjuvant therapy are recognized, but also that researchers are exploring more effective neoadjuvant options.

CONCLUSION

The advent of the era of combination therapy, represented by the "T-A regimen", has revolutionized the treatment of HCC and significantly improved survival and prognosis. By integrating the study of neoadjuvant therapy with the study of perioperative treatment and achieving patient-centered, personalized management of the entire disease process, it is possible to further reduce the recurrence and metastasis rates of patients after surgery and improve long-term survival. To improve late-stage efficacy, overcoming the problem of drug resistance is particularly important. In the future, updating drugs with different targets and mechanisms of action, exploring different combinations of combination therapies, and developing new technologies such as oncolytic viruses, cancer vaccines, and gene/cell therapies may help overcome drug resistance[59-61]. Optimization of the original neoadjuvant treatment regimen is as important as the use of the new treatment regimen in subsequent clinical practice. In any country or region, the burden of treatment for oncology patients is still an issue that has to be considered. Anti-tumor treatment options should take into account local policies and health insurance support to identify the most appropriate options for patients. Postoperative recurrence of HCC is still a sword of Damocles that affects the prognosis of patients, and neoadjuvant therapy offers new options for patients to develop individualized treatment plans. The development of neoadjuvant therapy based on clinical trials in advanced HCC still requires continuous research in the selection of patient indications, timing of therapeutic interventions, and specific treatment protocols. Further high-quality basic or clinical studies are expected to provide more in-depth theoretical and clinical guidance for the preoperative and even perioperative management of HCC and to improve the clinical benefit for patients.

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FOOTNOTES

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ORIGINAL ARTICLE

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Efficacy of fluorouracil combined with paclitaxel and oxaliplatin for the treatment of advanced gastric signet ring cell carcinoma

Mi Liu, Bei Feng, Na He, Rong Yan, Jie Qin

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Abstract

BACKGROUND

Gastric signet ring cell carcinoma (GSRC) is a distinctive type of gastric cancer. It is a mucus-secreting adenocarcinoma that may progress to distant metastasis at an early stage. Because of poor differentiation, aggressive invasion, rapid progression, and other high-risk characteristics, early surgical intervention should be prioritized.

AIM

To explore the clinical efficacy of fluorouracil (5-FU) combined with paclitaxel and oxaliplatin for the treatment of advanced GSRC.

METHODS

A total of 85 patients with advanced GSRC were selected between January 2020 and June 2021 and randomly divided into a control group (n = 42, receiving standard chemotherapy) and a treatment group (n = 43, receiving monotherapy with oxaliplatin, 5-FU, and paclitaxel). Patients in the treatment group received a 135 mg/m^2 infusion of paclitaxel for 3 hours, a 400 mg/m^2 infusion of calcium folate (or 200 mg/m^2 of levocalcium folate) for 2 hours, and an 85 mg/m^2 infusion of oxaliplatin for 2 hours. This was followed by a continuous intravenous infusion of 2200-2400 mg/m^2 5-FU for 46 hours using a portable pump.

RESULTS

The treatment group showed a median survival time of 11.7 months and an objective response rate (ORR) of 32.5%, significantly higher than the control group

($P < 0.05$). Serum carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and albumin levels were correlated with treatment effectiveness in advanced GSRC ($P < 0.01$), but total serum protein was not correlated ($P > 0.05$). Safety and survival were assessed in all patients. Short-term efficacy was evaluated in 66 patients, with a disease control rate of 89.4% and an ORR of 48.5%. Median progression-free survival was 7.0 months (95% confidence interval [CI]: 6.85-7.15), and median overall survival was 10.6 months (95%CI: 9.86-11.3). Primary grade III/IV adverse events included neutropenia (22.1%) and peripheral neurotoxicity (10.3%).

CONCLUSION

This treatment regimen is more effective for patients with advanced GSRC. Serum levels of CEA, CA19-9, and albumin predicted chemotherapy efficacy, while total protein concentration correlated minimally and insignificantly.

Key Words: Oxaliplatin; Tigio; Carcinoembryonic antigen; Carbohydrate antigen 19-9; Advanced gastric signet ring cell carcinoma

Core Tip: This study explored the clinical efficacy of fluorouracil combined with paclitaxel and oxaliplatin for the treatment of patients with advanced gastric signet ring cell carcinoma, and analyzed the role of serum carcinoembryonic antigen, carbohydrate antigen 19-9, albumin, and total protein levels in evaluating chemotherapy efficacy.

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INTRODUCTION

Gastric signet ring cell carcinoma (GSRC) is a highly malignant undifferentiated gastric cancer (GC) originating from the epithelial cells of the gastric mucosa. It is characterized by the production of a large amount of mucus by cancer cells, causing the nucleus to be pushed to one side by a large amount of cytoplasmic mucus, so that under the microscope, the cancer cells appear like a ring "seal ring shape," hence the name[1]. Although the overall incidence of GC has decreased in recent decades, the proportion of GRCC is increasing, reaching 35% to 45%[2]. The histological manifestations of GRCC are early spread, mainly in the mucosal layer or submucosal layer of the stomach. However, once the tumor penetrates the submucosa, its invasion is significantly enhanced, rapidly spreading to the muscle layer of the stomach, the serous layer, and nearby lymph nodes[3]. The progression of population aging has led to a significant increase in the incidence of GC. Clinical symptoms are often nonspecific, and it is typically diagnosed at an advanced stage. GSRC is a distinct subtype of mucinous adenocarcinoma that can present in the early stage of GC causing distant metastasis. GSRC is poorly differentiated, highly invasive, progresses rapidly, and exhibits other high-risk characteristics, making early surgical intervention critical. According to the guidelines of the World Health Organization, GSRC is histologically diagnosed by the presence of "signet ring" cells in > 50% of the tumor cells. The incidence of GSRC increased 10-fold between 1970 and 2000. Current studies suggest that the lymph node metastasis rate in early GSRC is low, and that the prognosis is generally favorable. However, compared with non-SRCC, advanced GSRC shows lower sensitivity to chemotherapy and has a poorer prognosis. There is a lack of appropriate standardized treatment options for advanced GSRC, and the sensitivity of patients to chemotherapy with fluorouracil (5-FU) in combination with paclitaxel and oxaliplatin remains unclear.

Multiple meta-analyses have shown that patients with locally advanced or metastatic GC can benefit from chemotherapy. However, patients and their families often discontinue treatment because due to concerns about adverse effects. This highlights the importance of timely evaluation of a patient's condition, identifying factors that are likely to affect prognosis, and determining which patients will benefit most from chemotherapy, all of which have significant clinical implications. Multiple studies have shown that blood clearance of biomarkers such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), albumin, and total protein have high diagnostic and prognostic value in cancer. However, further research is needed to confirm whether these parameters can be reliably used to monitor and evaluate the effect of chemotherapy[4]. A meta-analysis of randomized clinical trials in patients with advanced-stage oral and GC showed that palliative chemotherapy can not only reduce symptoms but also significantly improves the quality of life compared to optimal supportive care. According to the European Society for Medical Oncology guidelines, 5-FU plus cisplatin is recommended as the reference regimen for advanced GC. In Phase 3 trials, the docetaxel + cisplatin + 5-FU regimen was shown to be superior to the 5-FU + cisplatin regimen, but is not widely used because of its poor tolerance[5]. Paclitaxel has been shown to have comparable efficacy to docetaxel, with fewer adverse effects. As a third-generation platinum drug, oxaliplatin offers better safety and greater efficacy than cisplatin. The combination of 5-FU,

paclitaxel, and oxaliplatin (POF regimen) is reportedly as effective as first-line treatment for advanced GC with response rates ranging from 52.1% to 57.1%, median progression-free survival (PFS) of 7.1-9.2 months, and median overall survival (OS) of 11.6-11.7 months[6]. These findings suggest that paclitaxel-based treatment regimens are effective in treating advanced GSRC[7,8]. However, the efficacy and safety of treatments for advanced GSRC have not yet been systematically studied or evaluated.

The primary objective of this study was to comprehensively investigate the complex correlations among serum levels of CEA, CA19-9, albumin, and total protein, and their impact on chemotherapy outcomes in patients with advanced GSRC. Additionally, this study assessed the predictive potential of alterations in these biomarker levels to predict the efficacy of chemotherapy in this patient cohort. A key objective was to evaluate the clinical efficacy and safety profile of the POF regimen as a first-line treatment strategy for advanced GSRC.

MATERIALS AND METHODS

General information

Patients admitted at The First Affiliated Hospital of Xi'an Medical College (Xi'an, China) between January 2020 and June 2021, for the treatment of advanced GSRC, were included in the study. All patients met the following inclusion criteria: Confirmed diagnosis of advanced GSRC; ≥ 65 years of age; had not received chemotherapy or radiation therapy in the past month; Karnofsky Performance Status score ≤ 70; had normal routine hematuria, liver, and kidney function test outcomes; normal electrocardiogram; no serious comorbidities of important organs or contraindications to chemotherapy; and expected survival of 3 months or longer. Patients with infection, bleeding, or tissue trauma were excluded. The study protocol was approved by the Hospital Ethics Committee (Grant No. XYYFYLL-KTSB-2024-10), and all patients provided written informed consent prior to chemotherapy. Our research was carried out in accordance with the Convention in accordance with the Declaration of Helsinki.

The random number table method was used to divide the patients into two groups. We used the envelope method for grouping. Specifically, the envelope method means that the randomization scheme is stored in an opaque envelope; the envelopes are opened successively according to the order of enrollment, and the grouping of patients is determined according to the allocation scheme in the envelope. For example, in this study, the results can be divided into 85 envelopes and randomized: The paper grouping control group was put into the envelope marked with number 001, the paper grouping treatment group was put into the envelope marked with number 002, and the paper grouping control group was put into the envelope marked with number 003. The envelope was distributed to the research implementation personnel after the envelope packaging was completed. When the first patient appeared, the inclusion and exclusion criteria were used to determine whether the patient was included in the study. If so, envelope No. 001 was opened. At this time, the study object number of this patient was 001, and the group was the control group. There were 43 patients in the treatment group, including 26 males and 17 females aged 65-78 years, with a median age of 69 years. There were 11 patients with mucous adenocarcinoma with indolescular carcinoma, 23 patients with mucosal adenocarcinoma with indolescular carcinoma, 6 patients with moderate and low-differentiation adenocarcinoma with cytocellular carcinoma, 18 patients with initial treatment, and 27 patients who were retreated. A total of 18 patients underwent surgery and 28 had postoperative recurrence or metastasis, including 12 patients with liver metastasis, 8 patients with metastasis to the supraclavicular lymph nodes, and 27 patients with intraperitoneal lymph node metastasis. There were 42 patients in the control group, including 24 males and 18 females, with an age range of 65-79 years and a median age of 72 years. There were 10 patients with mucous adenocarcinoma with indolescular carcinoma, 18 patients with mucosal adenocarcinoma with indolescular carcinoma, 7 patients with moderate and low-differentiated adenocarcinoma with cytocellular carcinoma, 16 patients with initial treatment, and 16 patients with retreated disease. In total, 24 patients were not treated; 23 had postoperative recurrence or metastasis, 13 had liver metastasis, 10 had supraclavicular lymph node metastasis, and 18 had intraperitoneal lymph node metastasis. A comparison of the general data of the two patient groups revealed that the difference was not statistically significant ($P > 0.05$).

Follow-up and efficacy evaluation

Patients were examined for objective efficacy evaluation of chemotherapy following every three cycles of treatment. The baseline assessments included clinical history, comprehensive physical examination, Eastern Cooperative Oncology Group (ECOG) score, blood count, liver and kidney function, tumor marker levels, medical comorbidities, chest computed tomography (CT), abdominal and pelvic CT, and magnetic resonance imaging (MRI). Following every three cycles of treatment, patients were examined for objective efficacy evaluation of chemotherapy, for which they were divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) groups according to RECIST 1.1 evaluation. PFS was defined as the time from the initiation of chemotherapy to disease progression, death, or loss to follow-up for any reason. OS was defined as the time from the initiation of chemotherapy to death or loss to follow-up for any reason[9]. Adverse reactions were evaluated according to Common Terminology Criteria for Adverse Events v3.0 and classified as 0-IV.

Treatments

Control group: The POF regimen consisted intravenous infusions of 135 mg/m^2 paclitaxel for 3 hours, 400 mg/m^2 calcium folinic acid (levofalinate calcium 200 mg/m^2) for 2 hours, and synchronized oxaliplatin 85 mg/m^2 infusion for 2 hours, followed by continuous intravenous infusion of 5-FU (200-2400 mg/m^2) for 46 hours (using a portable pump) for 14 days. Efficacy was evaluated after every three cycles of treatment. Pretreatment with glucocorticoids, antihistamines,

and H_2 receptor antagonists was performed prior to paclitaxel infusion. Prophylactic administration of antiemetics was performed before the infusion of chemotherapeutic drugs[10]. During the treatment, measures were taken to keep the patients warm and to avoid exposure to cold stimuli. Granulocyte colony-stimulating factors were administered as needed, particularly in cases where leukocyte counts dropped below acceptable levels or neutropenia developed. In instances of treatment-related grade III/IV toxicity, the dosage for the subsequent chemotherapy cycle was reduced by 25%. Treatment was continued until one of the following occurred: Disease progression, development of intolerable toxicity, or the patient's decision to discontinue treatment.

In the treatment group, 5-FU was administered in combination with paclitaxel and oxaliplatin as follows: Oxaliplatin and 5-FU (Jiangsu Hengrui Pharmaceutical Co., Ltd.; 20 mg; Lot number: 16110496) were combined with a taxol injection (Ai Heng, 100 mg, batch number not provided; Jiangsu Hengrui Pharmaceutical Co., Ltd., Jiangsu, China). The dosing regimen included 130 mg/m^2, intravenously, on day 1 of each cycle, with each cycle spanning 21 days. Patients in both groups received minimum two cycles of chemotherapy, or 2-4 cycles if the disease did not progress[11].

Prior to chemotherapy, all patients were routinely administered antiemetics, such as tosane sparron, to prevent nausea and vomiting. Granulocyte colony-stimulating factor was administered if peripheral white blood cell count fell below the lower limit of normal post-chemotherapy.

Observation indicators and methods

One week before treatment and two cycles post-chemotherapy, the patient was examined *via* analysis of chest and abdomen CT, bone emission computed tomography, skull MRI, as well as serum CEA, CA19-9, albumin, and total protein levels. CT and other imaging assessments were performed every treatment two cycles. Enhanced CT scans were repeated to evaluate the immediate efficacy of the therapy. Assessments continued until disease progression was observed or the development of intolerable adverse drug reactions (ADRs) necessitated discontinuation of treatment.

The median survival time (MST) was calculated as the survival time based on a cumulative survival rate of 50% from the beginning of chemotherapy[12].

Treatment efficacy was assessed over a 4-week period based on RECIST 1.1 guidelines according to the following evaluation criteria: (1) CR: Complete disappearance of all lesions; (2) PR: Maintenance of at least one PR with an estimated tumor size shrinkage by more than 50% sustained for at least 4 weeks; (3) SD: After at least two treatment cycles (after 6 weeks), no significant change in the lesion size with an estimated tumor shrinkage of less than 50% or enlargement less than 25%; and (4) PD: Emergence of new lesions or tumor size increase exceeding 25%. The ORR included CR and PR, while the disease control rate (DCR) comprised CR, PR, and SD (CR + PR + SD).

The diagnostic reagents used for CEA, CA19-9, albumin, and total protein were purchased from Roche Diagnostic Reagent Company (Basel, Switzerland). Quality control was ensured as follows: CEA and CA19-9 measured using the electrochemiluminescence method, and albumin and total protein measured using the turbidity method. Blood parameters, liver and kidney function, electrolytes, serum markers (CEA, CA19-9, albumin, and total protein) were routinely reviewed before and after chemotherapy.

ADRs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events. Reactions were categorized into five grades, ranging from Grade 0 (no ADR) to Grade 5 (severe ADRs)[13].

Statistical analyses

The data were processed using Statistical Package for the Social Sciences software (version 26.0). OS and PFS were analyzed using the Kaplan-Meier method. Significance was analyzed using the log-rank test. $P < 0.05$ was considered statistically significant. The counting data were compared, and survival analysis was performed *via* Kaplan-Meier analysis, which included multilinear regression analysis of detection indicators and treatment efficacy.

RESULTS

Comparison of the prognosis and efficacy of chemotherapy in the two groups

The MST was 11.7 months in the treatment group and 10.0 months in the control group, and the difference was statistically significant ($P < 0.05$). The 1-year survival rate was 27.0% in the treatment group and 15.0% in the control group. After two chemotherapy cycles, the ORR was 32.5% in the treatment group and 19.0% in the control group, and the difference was statistically significant ($P < 0.05$). The clinical efficacies of these regimens are shown in Table 1.

Analysis of changes in serum indices pre- and post-chemotherapy and their correlation with treatment efficacy

Following chemotherapy, the serum CEA and CA19-9 Levels in the PR group were significantly lower than those before chemotherapy, and the serum albumin level was significantly higher ($P < 0.05$). The blood clearance of patients with PD increased before chemotherapy, and the serum albumin level decreased from that before chemotherapy ($P < 0.05$). There were no significant changes in serum CEA, CA19-9, albumin, or total protein levels in patients with SD compared with those before treatment ($P > 0.05$). Multiple linear regression analysis revealed that changes in serum CEA, CA19-9, and albumin concentrations were related to the efficacy of the chemotherapy for preventing cell carcinoma in advanced GSRC ($P < 0.01$); however, the total serum protein concentration was not significantly correlated with the efficacy of chemotherapy ($P > 0.05$; Table 2).

Table 1 Comparison of clinical efficacy between the two patient groups

Treatment prescription	Sample	PR	SD	PD	ORR (%)	DCR (%)
Control group	42	8	20	14	19	66.7
Treatment group	43	14	20	9	32.5	79.1

DCR: Disease control rate; ORR: Objective response rate; PD: Progressive disease; PR: Partial remission; SD: Stable disease.

Table 2 Analysis of the relationship between serum index expression levels and treatment efficacy before and after chemotherapy (mean ± SD)

Detect items	Patients with PR (*n* = 22)		Patients with SD (*n* = 40)		Patients with PD (*n* = 23)		*P* value
	Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy	
CEA (ng/mL)	28.5 ± 27.8	22.6 ± 21.6	24.8 ± 25.7	23.4 ± 22.5	32.8 ± 31.8	44.6 ± 34.8	< 0.01
CA19-9 (ng/mL)	145 ± 117	116 ± 91	159 ± 127	164 ± 136	166 ± 115	186 ± 145	< 0.01
Serum albumin (g/L)	267 ± 155	278 ± 193	409 ± 267	405 ± 260	470 ± 258	413 ± 256	< 0.01
Serum total protein (g/L)	569 ± 385	509 ± 314	548 ± 256	526 ± 215	587 ± 258	596 ± 274	> 0.05

CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; PD: Progressive disease; PR: Partial remission; SD: Stable disease.

Occurrence of ADRs

The most commonly observed ADRs included nausea, vomiting, leukopenia, and peripheral sensory reactions. These were managed with symptomatic treatment, and no chemotherapy-related deaths occurred during the study. The incidence of ADRs in the control group and treatment group was 16.7% and 18.6%, respectively, and this difference was not statistically significant ($P > 0.05$; Table 3).

Patient characteristics

Clinical characteristics of the 85 patients, who received the POF regimen from January 2020 to June 2021, are presented in Table 4. The safety and survival rates were evaluated in 83 patients.

Clinical efficacy

Two patients refused further chemotherapy because of grade IV neutropenia concomitant with infection, and objective efficacy was evaluated in 83 patients. Among them, 11 patients achieved CR (13.3%), 29 achieved PR (34.9%), 34 had SD (41.0%), 9 had PD (10.8%), and 48.1% had objective efficiency with 89.1% DCR (Table 5). The average follow-up time was 13.2 months, the median PFS was 7.0 months, and the median OS was 10.6 months. The PFS and OS curves are shown in Figure 1.

Incidence of adverse events

Safety was evaluated in all patients. Common hematological toxicities included grade I/II leukopenia (60.0%), neutropenia (38.8%), anemia (43.5%), grade III/IV neutropenia (22.4%), and total febrile neutropenia (2.9%). Common non-hematological toxicities included peripheral neurotoxicity (62.4%), liver function impairment (55.3%), and diarrhea (28.2%). The incidence rate of grade III/IV peripheral neurotoxicity was 10.6% (Table 6). No treatment-related deaths occurred.

DISCUSSION

The efficacy of chemotherapy in patients with SRCC remains questionable. A retrospective study showed lower response rates in SRCC patients compared to those with non-SRCC GC, although 12% of SRCC patients treated with taxane regimens had an improved outlook. In metastatic SRCC, response rates are low, with only 3% of patients responding to taxane-based chemotherapy[14]. Patients with mixed SRCC showed better survival after docetaxel combination chemotherapy. Among various regimens, FLOT (5-FU-leucovorin-oxaliplatin-docetaxel) chemotherapy provided greater benefit with fewer side effects than ECF/ECX (epirubicin + cisplatin + capecitabine) regimens, highlighting the potential of taxanes in SRCC. The TEFOX (triplet chemotherapy, with docetaxel-5FU-oxaliplatin) regimen is an effective first-line

Table 3 Occurrence of adverse drug reactions in the two groups of patients, *n* (%)

Treatment options	Nausea and vomiting	White blood cell decrease	Diarrhea	Peripheral sensation adverse reactions	Bone marrow suppression
Control group, *n* = 42	4 (9.5)	3 (7.14)	1 (2.38)	2 (4.76)	1 (2.38)
Treatment group, *n* = 43	5 (11.62)	2 (4.65)	2 (4.65)	3 (6.97)	1 (2.32)

Table 4 Clinical characteristics of 85 patients with advanced gastric signet ring cell carcinoma, *n* (%)

Characteristic	Value
Sex	
Women	50 (58.8)
Men	35 (41.2)
Age (year)	
Median	69
Range	65-78
ECOG	
0	48 (56.5)
1	28 (32.9)
2	9 (10.6)
Primary tumor site	
Esophagogastric junction	28 (32.9)
Gastric body/fundus	23 (27.1)
Gastric antrum	19 (22.4)
Leather stomach	15 (17.6)
Organs involved	
Lymph nodes	51 (60.0)
Liver	31 (36.4)
Lung	9 (10.6)
Peritoneum	30 (35.3)
Other	10 (11.8)
Number of organs involved	
1	23 (27.1)
2	33 (38.8)
> 2	29 (34.1)

ECOG: Eastern Cooperative Oncology Group.

treatment for advanced gastric SRCC with tolerable side effects. Paclitaxel and docetaxel are effective taxanes with few side effects[15]. Oxaliplatin, a third-generation platinum-based drug, has shown better efficacy and safety than cisplatin in gastric SRCC. The 2-week POF regimen as first-line therapy was effective, but associated with shorter PFS and OS than outcomes observed in general advanced GC. The poor prognosis of SRCC is due to its aggressive characteristics, which require specific treatment strategies. The POF regimen is safe and effective as first-line treatment for advanced gastric SRCC[16].

Chemotherapy is currently the primary treatment option for advanced GC. Oxaliplatin combined with capecitabine and docetaxel combined with oxaliplatin and tigio (Tegafur, Gemaemine and Otiracil potassium) have become the standard first-line treatment regimens for patients with advanced GC[17]. Oxaliplatin is a stable, water-soluble third-generation platinum compound, and it has demonstrated significant advantages in treating advanced GC. Compared to

Table 5 Efficacy data for 83 patients with advanced gastric signet ring cell carcinoma, *n* (%)

Parameter	Value
CR	11 (13.3)
PR	29 (34.9)
SD	34 (41.0)
PD	9 (10.8)
ORR	40 (48.1)
DCR	74 (89.1)

CR: Complete disappearance; DCR: Disease control rate; ORR: Objective response rate; PD: Progressive disease; PR: Partial remission; SD: Stable disease.

Table 6 Incidence of adverse events in patients with advanced gastric signet ring cell carcinoma after chemotherapy

Toxicity (NCI-CTCAE v 3.0)	Grade I	Grade II	Grade III	Grade IV	Grade I/II (%)	Grade III/IV (%)
Leukopenia	34	17	14	4	60.0	21.2
Neutropenia	20	13	15	4	38.8	22.4
Anemia	28	9	6	0	43.5	7.1
Thrombocytopenia	13	5	6	1	21.2	8.2
Nausea/vomiting	14	5	0	0	22.4	0
Diarrhea	20	4	0	0	28.2	0
Oral mucositis	5	3	5	0	9.4	5.9
Hepatic injury	29	18	4	0	55.3	4.7
Peripheral neurotoxicity	35	18	9	0	62.4	10.6
Anaphylaxis	0	0	0	0	0	0

NCI-CTCAE v3.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

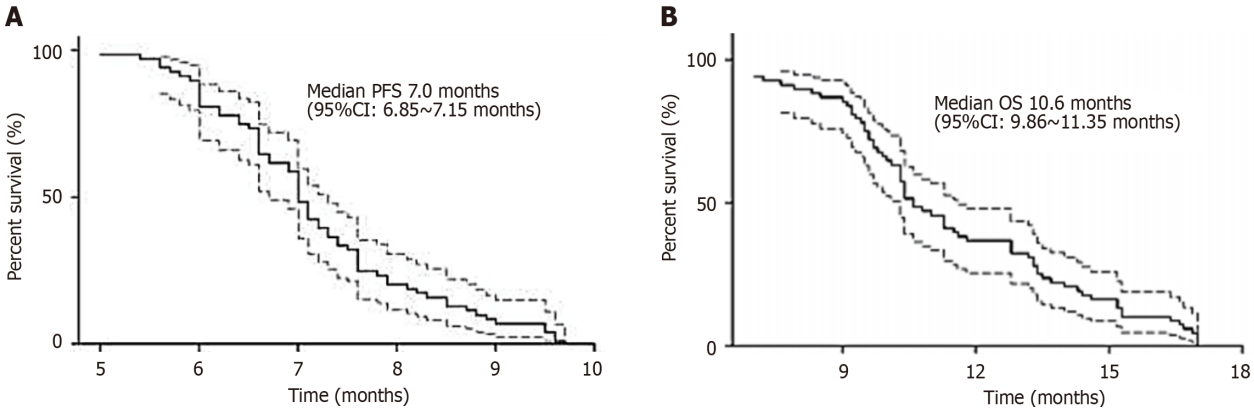

Figure 1 Patients (*n* = 85) with advanced gastric signet ring cell carcinoma. A: Progression-free survival curve (PFS); B: Overall survival time curve (OS).

cisplatin, oxaliplatin exhibits similar antitumor activity, but with significantly lower toxicity to the gastrointestinal tract and kidney, making suitable for patients with kidney disease. Tigio, an oral 5-FU formulation composed of tetrafluoride combined with gemmester and oteracil potassium has shown has a monotherapy efficacy of 26%-49%, comparable to that of continuous intravenous pumping of 5-FU. Furthermore, long-term use of centrally placed artisanal catheters can assist patients in preventing local discomfort, venous thrombosis, catheter-related infections, and the need for frequent care [18]. Presently, the evaluation of chemotherapeutic efficacy relies mainly on comparisons of tumor imaging before and after treatment. The differences in the expression of tumor-related biomarkers and the patient's nutritional status during

tumor progression and stabilization can, however, provide additional insights. These parameters enable rapid and accurate evaluation of treatment efficacy, which can help in optimizing therapeutic decisions and avoid delays in patient care.

Plasma albumin, synthesized in the liver, comprises 55%-65% of the total plasma proteins, and has a half-life of 21 days. It helps to maintain osmolality, transporting various plasma substances, and reflects protein nutritional status. In malnutrition, plasma albumin levels drop, triggering various dysfunctions. Serum albumin and transfer factor concentrations are vital parameters in nutritional assessment. A decline in total protein is associated with malnutrition, cachexia, cirrhosis, malignancy, and other chronic wasting diseases[19].

Older patients with advanced GC often experience reduced body function, chronic diseases, and poor tolerance to chemotherapy. Studies indicate that palliative chemotherapy can benefit these patients by improving their symptoms and survival without significantly increasing the incidence of adverse reactions. A study found an ORR of 32.5% and an MST of 11.7 months, similar to younger patients, suggesting effectiveness of chemotherapy[20]. CEA and CA19-9 are crucial markers for monitoring prognosis in GC. CEA, an acidic glycoprotein associated with colon cancer, and CA19-9, a glycolipid tumor antigen, shown to be correlate with survival outcomes. Positivity of these tumor markers predict worse outcomes, and their combined evaluation enhances diagnostic accuracy[21]. Abnormal protein and amino acid metabolism are hallmarks of tumors, with higher rates of histone conversion observed. Post-chemotherapy, CEA and CA19-9 levels were found to decline in responders, whereas albumin levels increased. In contrast, the non-responders showed higher CEA levels and lower albumin levels. CA19-9 and total protein levels remained stable in both groups. CEA, CA19-9, and albumin levels correlate with chemotherapy efficacy, whereas changes in total protein levels do not. Thus, monitoring these markers can predict chemotherapy response, aiding in the diagnosis and prognosis in advanced GSRC[22].

This study suggests that serum CEA, CA19-9, and albumin concentrations can be used to predict the efficacy of chemotherapy in patients with advanced GSRC[23]. There was no statistically significant correlation between total serum protein concentration and the efficacy of chemotherapy. However, due to the limited number of patients in this study, it is necessary to expand the sample size for further in-depth studies.

Study limitations

Our study had some limitations. First, the patient population included in the study was generally in good health, with only 11.8% of patients having an ECOG score of 2, and 26.5% of patients with single-onset distant metastases. Second, this was a retrospective study in which the POF regimen was compared with other regimens (paclitaxel with oxaliplatin and cisplatin with 5-FU regimen) as the first-line treatment of advanced gastric SRCC. However, the safety and efficacy of these regimens require further validation through prospective studies.

CONCLUSION

In conclusion, our study demonstrated that the chemotherapy regimen was effective in prolonging survival and improving the prognosis of patients with advanced GSRC. Changes in serum CEA, CA19-9, and albumin concentrations were significantly correlated with the efficacy of chemotherapy. Although ADRs were observed, they were manageable, and no chemotherapy-related deaths occurred. These findings provide valuable insights into the treatment of advanced GSRC and suggest that the chemotherapy regimen may be a promising option for these patients. In recent years, the application of immunotherapy for treatment of GC has emerged as significant area of research. Notably, 40.4% of the patients with SRCC demonstrated positivity for Programmed cell death ligand 1 (PD-L1), highlighting the potential of anti-programmed cell death protein 1 (PD-1)/PD-L1 therapy as a promising approach. First-line treatment with the POF regimen is safe and effective for patients with advanced GSRC. However, the potential of combining the POF regimen with anti-human epidermal growth factor receptor 2-targeted therapy and/or anti-PD-1/PD-L1 immunotherapy in patients with advanced GSRC deserves further exploration.

FOOTNOTES

Author contributions: Qin J designed the study; Liu M wrote the original draft; Feng B, He N, and Yan R collected the raw data; Yan R performed the statistical and bioinformatics analyses; Qin J supervised the study; All authors have read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Combined application of the preclosure technique and traction approach facilitates endoscopic full-thickness resection of gastric submucosal tumors

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Abstract

BACKGROUND

Gastrointestinal submucosal tumors (SMTs) mostly grew in the lumen, but also some of the lesions were extraluminal, in which the stomach was the most common site. Gastrointestinal stromal tumor account for a large proportion of SMT. Due to the deep lesion location of gastric SMT, endoscopic submucosal dissection related techniques are difficult to operate, while endoscopic full-thickness resection (EFTR) has been widely used in clinical practice because it is less invasive and can preserve the physiological structure and function of the stomach. However, complete closure of the gastrectomy site after EFTR is critical. If the closure is incomplete, it may cause peritonitis, late perforation and other conditions, and even require further surgical intervention. Although there are currently a number of suture devices and techniques that can be used to promote closure, they have the problem of requiring additional equipment or being inconvenient to use. Although metal clips are widely used, their effectiveness depends on the size and tension of the defect. Therefore, an effective and convenient endoscopic closure technique is urgently needed to solve the closure problem of gastric SMTs after treatment.

AIM
To investigate the effect of combined application of the preclosure technique and dental floss traction in gastric wound closure following EFTR.

METHODS
In this study, the data of 94 patients treated for gastric SMTs at the Gastrointestinal Endoscopy Center of the Affiliated Union Hospital of Fujian Medical University from April 2022 to May 2023 were retrospectively analyzed. The patients were divided into a preclosure group (54 patients) and a non-preclosure group (40 patients) on the basis of the timing of wound closure with titanium clips after dental floss traction-assisted EFTR. Each patient in the preclosure group had their wounds preclosed with titanium clips after subtotal lesion resection, whereas each patient in the non-preclosure group had their wounds closed with titanium clips after total lesion resection. The lesion size, wound closure time, number of titanium clips used, incidence of postoperative complications, and postoperative hospitalization time were compared between the two groups.

RESULTS
The wound closure time was significantly shorter in the preclosure group than in the non-preclosure group (6.69 ± 2.109 minutes *vs* 11.65 ± 3.786 minutes, $P < 0.001$). The number of titanium clips used was significantly lower in the preclosure group (8.93 ± 2.231) than in the non-preclosure group (12.05 ± 4.495) ($P < 0.001$). There was no significant difference between the two groups in terms of the need for an indwelling gastric tube or the length of postoperative hospital stay (6.41 ± 1.31 *vs* 6.13 ± 1.06 days). For all patients in the preclosure group and the non-preclosure group, resection was completed successfully without bleeding, abdominal pain, abdominal distension, or other postoperative complications.

CONCLUSION
Application of the preclosure technique combined with dental floss traction can be used intraoperatively to effectively close the surgical wound in patients undergoing EFTR, reliably preventing the tumor from falling into the peritoneal cavity.

Key Words: Gastric submucosal tumor; Dental floss traction; Endoscopic full-thickness resection; Preclosure technique

Core Tip: Using the endoscopic full-thickness resection (EFTR) technique to treat gastric submucosal tumors, the use of external dental floss traction with endoscopic therapy can provide a clearer surgical field, thereby reducing surgical difficulty and the risk of intraoperative bleeding. In EFTR, the preocclusion technique combined with dental floss traction can effectively close the defect, effectively prevent the tumor from falling into the abdominal cavity. This approach is undoubtedly a reliable defect closure method.

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INTRODUCTION

Gastrointestinal submucosal tumors (SMTs) are protuberant lesions that originate in the muscularis mucosa, submucosa, or muscularis propria (including gastrointestinal leiomyomas, Brunner's gland adenomas, granulosa cell tumors, lipomas, schwannomas, glomus tumors and ectopic pancreatic tissue); some of these lesions are extraluminal[1]. The incidence rates of SMTs in various parts of the digestive tract differ; however, the stomach is the most common site for SMTs in the digestive tract[2]. According to relevant expert guidelines, endoscopic surgical resection of small-diameter gastric SMTs can be considered when endoscopic techniques are available and patients are willing to receive radical treatment[3]. However, for gastric SMTs with a diameter of less than 10 mm, endoscopic submucosal dissection (ESD) and the related techniques are too complicated and difficult to perform. In recent years, endoscopic full-thickness resection (EFTR) has been increasingly widely used to treat patients with small-diameter gastric SMTs[4], thereby achieving a complete resection rate of 100% and extremely low complication rates[5]. However, proper closure of the perforation site after EFTR is key to the success of this approach. On this basis, in this study, 'preclosure' was investigated. Preclosure is a procedure by which, after dental floss traction-assisted EFTR for a gastric SMT, the wound is first preclosed with titanium clips before lesion excision. In this study, preclosure shortened the wound closure time and reduced the number of

titanium clips used.

MATERIALS AND METHODS

Data sources

In this study, the data of 94 patients treated with EFTR for gastric SMTs by a skilled endoscopist at the Gastrointestinal Endoscopy Center of the Affiliated Union Hospital of Fujian Medical University from April 2022 to April 2023 were retrospectively analyzed. In this study, to exclude interoperator differences, all operations were performed by the same endoscopist with the same equipment. The inclusion criteria were as follows: (1) Patients with gastric SMTs diagnosed by conventional endoscopy, endoscopic ultrasonography (EUS), computed tomography (CT) or other imaging examinations [3]; (2) Patients with gastric SMTs with diameters ≤ 2 cm found to originate from the gastric submucosa or muscularis propria by EUS[6]; (3) Patients who were 32-78 years in age; (4) Patients with single lesions; and (5) Patients with tumor sites restricted to the gastric body, gastric fundus and gastric fundus-body junction. The exclusion criteria were as follows: (1) Patients with severe cardiovascular or cerebrovascular diseases; (2) Patients with abnormal coagulation function; (3) Patients with metastasized tumors; (4) Patients exhibiting tumors with a diameter > 2 cm; and (5) Patients who refused endoscopic treatment. The patients were grouped on the basis of the timing of wound closure with titanium clips after dental floss traction-assisted EFTR. Patients in whom the wound was preclosed with titanium clips after subtotal lesion resection before receiving complete wound closure were included in the preclosure group (54 patients), and patients in whom the wound was closed with titanium clips after total lesion resection were included in the non-preclosure group (40 patients). There was no significant difference in sex, age, history of hypertension, history of diabetes mellitus, or history of abdominal surgery between the two groups ($P > 0.05$) (Table 1). This study was approved by the Medical Ethics Committee of the Affiliated Union Hospital of Fujian Medical University. All patients completed relevant examinations after admission, were fully informed before surgery, and signed a consent form for endoscopic treatment.

Instruments

The following table provides information regarding the endoscope and related instruments (Table 2).

Treatment methods

Preoperative preparation: Antipyretic, analgesic, antiplatelet and anticoagulant drug treatments were discontinued one week before surgery, and a complete blood count and coagulation tests (PLT, FIB, and DD) were performed. The pre-endoscopic preparation was the same as the gastrointestinal preparation for conventional endoscopy. All patients underwent endoscopic surgery under general anesthesia.

Surgical methods: (1) Marking and injection: The edge of the lesion was marked by electrocoagulation using a dual knife. Submucosal injections were performed outside the marked point on the anal side. Care was taken to limit the amount of material injected to 1 mL; slight elevation of the mucosa at each lesion was sufficient; (2) Incision: The mucosa and submucosa around the tumor were incised with a dual knife in a semicircular manner to expose part of the tumor; (3) Installation of the dental floss traction device: The gastroscope was first withdrawn, and then the clip device was inserted through the forceps channel of the gastroscope. The dental floss was fixed on one arm of the clip device *via* the double-knot method. After entry of the gastroscope, the clip device with dental floss was clamped at the incisal edge of the lesion, and the lesion was pulled upward by moderate traction using the hemostatic forceps to fully expose the submucosa and thereby obtain a clear operating field of view (FOV); (4) Full-thickness resection and preclosure: The intrinsic muscular and plasma layers around the tumor were incised with a dual knife under dental floss traction, creating an "active" perforation of the gastric wall and detaching most of the tumor. The gastric wall defect was linearly lifted by external traction with dental floss. Preclosure of the gastric wall wound was performed with a clip device to prevent the tumor from falling into the abdominal cavity and to minimize excessive tension on the gastric wall defect after the tumor had been completely excised; and (5) Complete resection and closure: The remaining gastric wall defect was closed by using the clip device after the tumor was completely resected with the IT knife. EFTR of a gastric SMT (Figure 1).

Specimen processing: Fresh, completely resected SMT specimens were rinsed and spread out to observe, measure and record the characteristics (size, shape, color, hardness, integrity of the capsule, *etc.*) of each. The samples were then placed in formaldehyde for pathological examination[1,3].

Postoperative treatment: All patients received oxygen (inhaled) and were monitored by ECG after surgery, and their vital signs were closely monitored. The patients rested in a semirecumbent position. After fasting for 3-4 days after the operation, the patients were assessed for abdominal pain, abdominal distension, hematemesis, and fever. Routine acid suppression, fluid replacement, and nutritional support were provided. If an indwelling gastrointestinal decompression tube was placed, the tube was properly managed.

Observation indicators: The wound closure time, number of titanium clips used during the operation, length of postoperative hospital stay, tumor size, pathological results, and number of postoperative fasting days were recorded for the two groups of patients.

Table 1 Comparison of the baseline data of patients in the preclosure and non-preclosure groups

Group	Sex (patients)		Age (years) (mean ± SD)	Hypertension (cases)	Diabetes mellitus (case)	History of abdominal surgery (case)
	Male	Female				
Preclosure group	22	32	57.13 ± 10.37	13	2	14
Non-preclosure group	16	24	54.18 ± 8.44	6	3	9
χ^2/t value	0.005		1.475	1.173	0.120	0.146
P value	0.942		0.144	0.279	0.729	0.702

Table 2 The endoscope and related instruments

Instrument name	Model	Manufacturer
Gastroscope host	EPK-i7000	PENTAX
Electronic upper gastrointestinal endoscope	EG29-i103.2	PENTAX
High-frequency electric cutting device	VI200S	ERBE
CO_2 insufflator	UCR	Olympus
IT knife	KD-612 L	Olympus
Dual knife	KD-650 L	Olympus
Transparent cap	D-201-11804	Olympus
Thermal biopsy forceps	HDBF-2.4-230-S	COOK
Injection needle	VIN-23	COOK
Electric snare	AG-5072-242523	AGS MedTech
Clip device	AG-51042-1950-135-16	AGS MedTech
Irrigation pump	MD4-185	AOHUA

Statistical analysis

SPSS 27.0 statistical software was used for statistical analyses. Normally or approximately normally distributed data are expressed herein as mean ± SD, and count data are expressed as the rate or composition ratio. Measurement data were compared between the two groups by using the *t* test or *t* test, and count data were compared between the two groups *via* the χ^2 test. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Intraoperative and postoperative results

The average size of the tumors in 94 patients diagnosed by EUS and CT was 1.13 cm (0.3-1.9) cm (Figure 2). One tumor was located in the posterior wall of the cardia (1%), 50 tumors were located in the gastric fundus (53.2%), 33 tumors were located in the gastric body (35.1%), 2 tumors were located in the gastric antrum (2.1%), 1 tumor was located in the gastric angle (1%), 6 tumors were located in the fundus-gastric body junction (6.4%), and 1 tumor was located in the ridge between the gastric body and the fundus (1%) (Table 3). All patients completed EFTR treatment, and the operation success rate was 100.0%. The wound closure time and number of titanium clips used were significantly lower in the preclosure group than in the nonclosure group ($P < 0.05$); the number of fasting days, length of postoperative hospital stay, and need for an indwelling gastric tube did not significantly differ between the two groups (Table 4). The average wound closure time was 8.8 minutes (3-20 minutes). The average hospital stay was 6 days (4-9 days), and no delayed bleeding or peritonitis symptoms occurred during hospitalization.

Pathological results

All specimens were sent for pathological analysis. All 94 specimens were obtained *via* EFTR, the mucosal surface and serosal surface of the tumor were clearly visible, and no residual tumor or ectopic pancreatic tissue was found at the resection margin of all lesion tissues, indicating a complete resection rate of 100.0%. Pathological analysis revealed 73 (77.7%) cases of stromal tumors, 14 cases (14.9%) of leiomyomas, 2 cases (2.2%) of calcified fibrous tumors, 1 case (1%) of

Table 3 Tumor sites in the two groups of patients

Group	Tumor site [*n* (%)]						
	Gastric body	Gastric fundus	Fundus-gastric body junction	Posterior wall of the cardia	Ridge between the gastric body and fundus	Gastric angle	Gastric antrum
Preclosure group (*n* = 54)	19 (35.2)	32 (59.2)	3 (5.6)				
Non-preclosure group (*n* = 40)	14 (35.0)	18 (45.0)	3 (7.5)	1 (2.5)	1 (2.5)	1 (2.5)	2 (5.0)

Table 4 Comparison of surgical conditions between the two groups of patients

Group	Wound closure time (min)	Number of titanium clips used (pcs)	Number of fasting days (days)	Length of postoperative hospital stay (days)	Need for an indwelling gastric tube [*n* (%)]
Preclosure group (*n* = 54)	6.69 ± 2.10	8.93 ± 2.23	3.61 ± 0.78	6.41 ± 1.31	9 (16.7)
Non-preclosure group (*n* = 40)	11.65 ± 3.78	12.05 ± 4.49	3.73 ± 0.84	6.13 ± 1.06	13 (32.5)
χ^2/t value	7.479	4.043	0.672	1.116	3.213
P value	< 0.001	< 0.001	0.504	0.267	0.073

Table 5 Pathological results for the two groups of patients

Group	Pathological type [*n* (%)]						
	Gastrointestinal stromal tumor	Leiomyoma	Ectopic pancreatic tissue	Calcified fibrous tumor	Spindle cell tumor	Schwannoma	Lipoma
Preclosure group (*n* = 54)	43 (79.6)	7 (12.9)		2 (3.7)		1 (1.9)	1 (1.9)
Non-preclosure group (*n* = 40)	30 (75.0)	7 (17.5)	1 (2.5)		1 (2.5)	1 (2.5)	

ectopic pancreatic tissue, 1 case of a spindle cell tumor (1%), 2 cases (2.2%) of schwannomas, and 1 case (1%) of lipoma (Table 5).

DISCUSSION

With advances in endoscopic and EUS techniques and increased health awareness, the rate of detection of gastrointestinal SMTs has increased significantly[7]. Generally, the clinical symptoms of SMTs with a diameter of less than 2 cm are not obvious, and such SMTs are mostly discovered incidentally during endoscopic examinations. In the past, regular endoscopic follow-up was generally recommended for patients with such gastric SMTs[1]. However, some gastric SMTs are capable of malignant transformation, and regular endoscopy places not only an economic burden but also great psychological pressure on patients[8]. With disease progression or lesion growth, some types of SMTs, including those that occur at certain sites, may cause abdominal pain, bleeding and obstruction[1,9]. Consequently, some doctors and patients prefer tumor resection over conservative treatment or regular follow-up.

In recent years, ESD-based EFTR has gradually become an emerging method for treating gastric SMTs. EFTR is an endoscopic surgery in which active perforation is used for full-thickness resection of the diseased gastric wall, regardless of the tumor depth. Compared with laparoscopic and laparotomic surgery, EFTR is less traumatic, and patients recover faster after surgery[10]. Andalib *et al*[11] reported 25 cases of patients with gastric SMTs treated with EFTR, achieving a complete resection rate of 100% and a complete suture rate of 100%. The surgical success rate in this study was 100%, which is consistent with that reported by Zhang *et al*[12] in a similar study.

During EFTR surgery, it is crucial to ensure that the perforation site is properly closed. A variety of closure methods are available to achieve this aim. For small defects, metal clips can be directly used for closure. However, larger defects require much more complete closure with highly complicated defect closure devices or instruments. In recent years, several novel methods, such as over-the-scope clip and OverStitch closure, have been applied to repair gastrointestinal damage and bleeding[13-15]. In addition, full-thickness resection devices, which combine EFTR and closure, have also been used. Although many methods and devices have been developed in recent years for gastrointestinal wall closure,

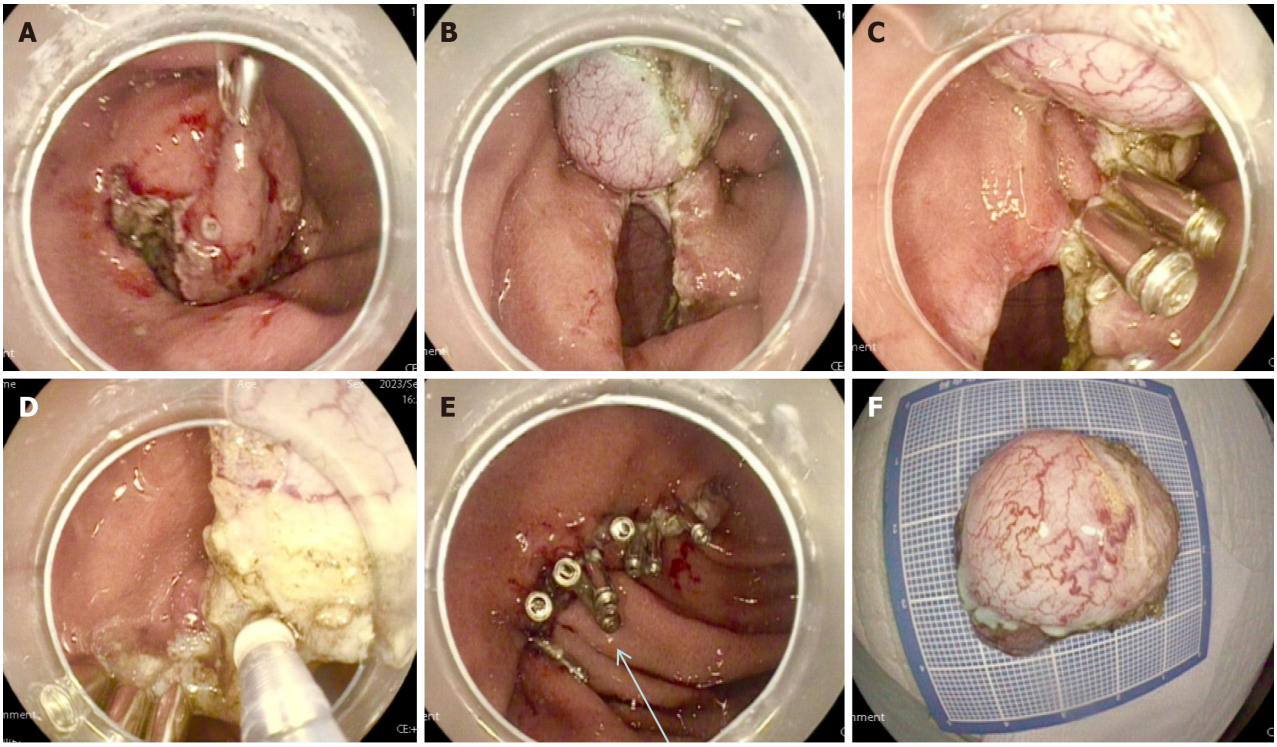

Figure 1 Endoscopic full-thickness resection procedure for a submucosal tumor, and the wound was preclosed with titanium clips before the lesion was completely removed. A: Giant gastric submucosal tumor found after stripping the mucosa and submucosa; B: Full-thickness resection around the tumor *via* the dental floss traction method; C: Preclosure of the gastric wound with clips once most of the tumor had been excised; D: Dissection of the remaining tumor tissue; E: Complete closure of the gastric wound with titanium clips; F: The full-thickness gastric wall surrounding the tumor is visible to the naked eye in this specimen.

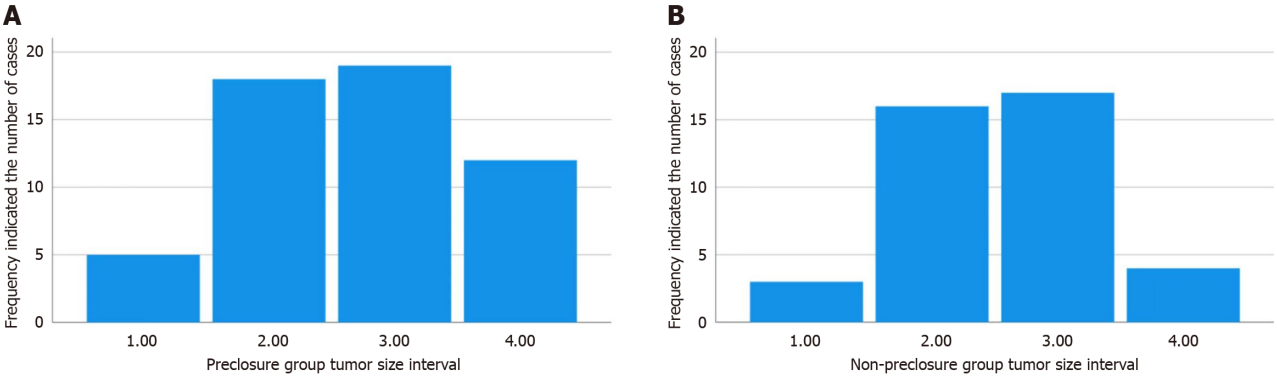

Figure 2 Tumor sites in the two groups of patients. A: The size and number of the tumors in the preclosure group of patients; B: The size and number of the tumors in the non-preclosure group of patients. 1 representation 0-0.5 cm. 2 representation 0.5-1 cm. 3 representation 1-1.5 cm. 4 representation 1.5-2 cm.

most of these methods require complex or specialized equipment and are technically challenging. Thus, given its simplicity, metal clip closure still plays an important role in wound closure in EFTR.

In our study, 94 patients with gastric SMTs underwent EFTR surgery. It is critical to maintain a clear endoscopic FOV during surgery. However, once the gastric wall is actively perforated, the FOV becomes limited, seriously impacting the surgical process. To solve this problem, Jeon *et al*[16] were first to report the use of dental floss-assisted ESD for the treatment of gastric mucosal lesions, in 2009. This method not only improves the view of the operational field but also achieves good results in practical applications. Soga *et al*[17] subsequently applied extracorporeal dental floss traction to EFTR in the treatment of gastric SMTs and achieved satisfactory results. During full-thickness resection in EFTR, the titanium clips are pulled by the dental floss to reduce the defect to a line, not only reducing the tension on the defect but also making it easier to close with the titanium clips, thus shortening the closure time[18]. This method requires only titanium clips and dental floss, which are common clinical endoscopic items that are easy to obtain, simple to use, and inexpensive. In this study, we demonstrated that with the assistance of dental floss traction, the gastric wall defect could be closed before complete tumor resection. This technique is simple and effective, and it is superior to using complex or specialized devices alone to close defects after EFTR. The advantages of this new technology are reflected in four main

aspects. First, the defect can be effectively closed by dental floss traction. Second, closing the defect before complete tumor detachment can effectively prevent the tumor from falling into the abdominal cavity both before and after complete tumor resection. Third, pseudo-occlusion due to inversion of the incision folds after complete tumor resection can be effectively prevented. Finally, the tension of the surrounding tissues and the entry of gas into the abdominal cavity can be significantly reduced, thereby reducing related complications and shortening the duration of the operation. These conclusions are consistent with those of relevant domestic studies.

CONCLUSION

In summary, when the EFTR technique is used to treat gastric SMTs, the use of external dental floss traction with endoscopic therapy can provide a clearer surgical field, thereby reducing surgical difficulty and the risk of intraoperative bleeding. In EFTR, the preocclusion technique combined with dental floss traction can effectively close the defect, effectively preventing the tumor from falling into the abdominal cavity. This approach is undoubtedly a reliable defect closure method. However, this study has several limitations. In the comparative analysis of the tumor size of the two groups, although the average size of the two groups was similar, individual large tumors may have existed in the common EFTR group, which may have had some impact on the wound closure time and the number of clips. Larger resected tumors may require more time and clips for closure. The preclosure technique in this study somewhat mitigated this difference, but further sample size expansion is needed to assess the effect of tumor size on surgical outcomes more accurately. Moreover, this was a single-center retrospective study with a relatively small sample size and possible selection bias. Therefore, these conclusions remain to be further verified and discussed in larger studies. Nevertheless, this study provides novel ideas and methods for the treatment of gastric SMTs and may help improve the treatment efficacy and patients' quality of life.

FOOTNOTES

Author contributions: Zu QQ, Chen FL study concept and design; You Y, Wang XR, Chen AZ, Zu QQ, Liu M acquisition of data; Zhang SH, You Y, Wang XR, Chen AZ, Zu QQ analysis and interpretation of data; Zu QQ, Chen FL drafting of the manuscript; Zu QQ, You Y, Wang XR, Chen AZ, Liu M, Chen FL critical revision of the manuscript for important intellectual content; Zu QQ, Zhang SH, Chen FL technical material support; Zu QQ, Liu M study supervision. All authors reviewed the results and approved the final version of the manuscript. Chen FL and Liu M played key roles at different stages of the study. One of them put a lot of effort into the experimental design and data collection phase, ensuring the scientific and reliable study. The other has made outstanding contributions to paper writing and theoretical analysis, which has improved the academic depth and readability of the paper. Their joint efforts have refined the results of this research, so co-serving as corresponding authors is a fair recognition of their contributions.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Union Hospital, Fujian Medical University.

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ORIGINAL ARTICLE

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Impact of diabetes on recovery after radical gastrectomy for gastric cancer: A retrospective cohort study

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Abstract

BACKGROUND

Gastric cancer remains a significant global health concern. Radical gastrectomy is the primary curative treatment. Diabetes mellitus is a common comorbidity in patients undergoing surgery for gastric cancer, including radical gastrectomy. Previous studies have suggested that diabetes can negatively affect postoperative outcomes, such as wound healing, infection rates, and overall recovery. However, the specific impact of diabetes on recovery after radical gastrectomy for gastric cancer remains poorly understood. evaluate the influence of diabetes on postoperative recovery, including hospital stay duration, complications, and readmission rates, in patients undergoing gastrectomy for gastric cancer. Understanding these effects could help optimize perioperative management and improve patient outcomes.

AIM

To investigate the impact of diabetes on recovery after radical gastrectomy for gastric cancer and associated postoperative outcomes.

METHODS

This retrospective cohort study was performed at the Endocrinology Department of Xuanwu Hospital, Capital Medical University, Beijing, China. We examined patients who underwent radical gastrectomy for cancer between January 2010 and December 2020. The patients were divided into the diabetes and non-diabetes groups. The main outcomes included length of hospital stay, postoperative complications, and 30-day readmission rate. Secondary outcomes included quality of life indicators. Propensity score matching was used to adjust for potential confounding factors.

RESULTS
A total of 1210 patients were included in the study, with 302 diabetic patients and 908 non-diabetic patients. After propensity score matching, 280 patients were included in each group. Diabetic patients demonstrated significantly longer hospital stays (mean difference 2.3 days, 95%CI: 1.7-2.9, $P < 0.001$) and higher rates of postoperative complications (OR 1.68, 95%CI: 1.32-2.14, $P < 0.001$). The 30-day readmission rate was also higher in the diabetic group as compared to the non-diabetic group (12.5% *vs* 7.8%, $P = 0.02$).

CONCLUSION
Patients with diabetes mellitus undergoing radical gastrectomy for gastric cancer experience prolonged hospital stay, increased postoperative complications, and higher readmission rates, thus requiring optimized perioperative management strategies.

Key Words: Gastric cancer; Diabetes mellitus; Radical gastrectomy; Postoperative recovery; Complications

Core Tip: This study evaluated the effect of diabetes mellitus on postoperative recovery in patients with gastric cancer who underwent radical gastrectomy. Diabetic patients experienced longer hospital stays, higher rates of postoperative complications, and increased 30-day readmission rates than non-diabetic patients. These results underscore the importance of tailored perioperative management strategies to improve the outcomes of patients with diabetes undergoing surgical interventions. Optimal care is essential to mitigate the adverse effects of diabetes on recovery following gastrectomy.

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INTRODUCTION

Gastric cancer remains the fifth most common malignancy and third leading cause of cancer-related deaths worldwide, with an estimated 1089103 new cases and 768793 deaths in 2020[1]. Despite advancements in early detection and treatment modalities, the prognosis of patients with gastric cancer remains poor, with a 5-year survival rate of approximately 30% in most countries[2]. Radical gastrectomy combined with appropriate lymphadenectomy continues to be the cornerstone of curative treatment for gastric cancer[3].

The outcomes of radical gastrectomy can be significantly influenced by various factors, including comorbidities. Diabetes mellitus, a chronic metabolic disorder characterized by persistent hyperglycemia, is a comorbidity that has garnered increasing attention in recent years. The global prevalence of diabetes has been rising steadily, with an estimated 463 million adults living with diabetes as of 2019. This figure is projected to reach 700 million by 2045[4].

The relationship between diabetes and cancer has been extensively researched, with evidence suggesting that diabetes may increase the risk of various cancers, including gastric cancer[5]. Moreover, diabetes has been associated with poorer outcomes in patients with cancer, including increased mortality and reduced quality of life (QOL)[6]. However, the specific effects of diabetes on recovery after radical gastrectomy for gastric cancer remain unclear.

Several molecular and cellular mechanisms underlie the adverse effects of diabetes on postoperative recovery. At the molecular level, chronic hyperglycemia leads to the formation of advanced glycation end products, which impair collagen synthesis and crosslinking, compromising wound healing[7]. Diabetes-induced microvascular dysfunction is characterized by reduced endothelial nitric oxide production and increased oxidative stress, which compromises tissue perfusion and oxygenation. Furthermore, diabetes impairs immune function through multiple pathways, including decreased neutrophil chemotaxis and phagocytosis, impaired T-cell responses, and dysregulated cytokine production[8].

Previous studies investigating the effects of diabetes on the outcomes after gastric cancer surgery have yielded conflicting results. Some studies have reported increased postoperative complications and mortality in patients[9,10], whereas other studies have found no significant differences[11,12]. These inconsistencies may be attributed to variations in study design, sample size, and definition of diabetes-related outcomes.

Given the high prevalence of both gastric cancer and diabetes, particularly in aging populations, understanding the interplay between these conditions is crucial for optimizing patient care and improving patient outcomes. This knowledge can inform preoperative risk assessment, guide perioperative management strategies, and assist in postoperative care planning for patients with diabetes undergoing radical gastrectomy.

This study aimed to address this knowledge gap by conducting a comprehensive analysis of the effects of diabetes on recovery after radical gastrectomy for gastric cancer.

MATERIALS AND METHODS

Study design and patient population

We performed a retrospective cohort study using data from Xuanwu Hospital, Capital Medical University, China, a large tertiary medical center with a high volume of cancer surgeries. This study was approved by the Ethics Committee of the Xuanwu Hospital, Capital Medical University, and informed consent was obtained from all participants. All patients who underwent radical gastrectomy for histologically confirmed gastric adenocarcinoma between January 1, 2010 and December 31, 2020 were eligible for inclusion. Exclusion criteria were: Age < 18 years, palliative or non-curative intent surgery, concurrent malignancies, incomplete medical records, and loss to follow-up within 30 days of surgery.

Data collection

Patient data were extracted from electronic medical records and the hospital's gastric cancer database following a standardized protocol. Two trained research assistants independently extracted the data and any discrepancies were resolved through discussion with a senior researcher. Data quality was ensured through regular audits of 10% of the randomly selected records. For missing data, defined as data present in < 5% of cases, multiple imputations using chained equations were performed with 20 iterations, including all baseline characteristics, treatment variables, and outcomes in the imputation model. Information collected from each patient included: (1) Demographic characteristics of age, sex, body mass index (BMI), smoking status, and alcohol consumption; (2) Comorbidities including hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease; (3) Diabetes-related data including duration of diabetes, type of diabetes (type 1 or 2), glycated hemoglobin (HbA1c) levels, and diabetes medication; (4) Tumor characteristics including TNM stage (according to the 8th edition of the American Joint Committee on Cancer staging system), tumor location, and histological type; (5) Surgical details including type of gastrectomy (total or subtotal), extent of lymphadenectomy, operative time, and estimated blood loss; and (6) Perioperative management including use of neoadjuvant or adjuvant therapy, antibiotic prophylaxis, and venous thromboembolism prophylaxis.

Definition of diabetes mellitus

Patients were classified as having diabetes mellitus if they met one or more of the following criteria: (1) Documented diagnosis of diabetes in medical records; (2) Use of antidiabetic medications (oral agents or insulin) at the time of hospital admission; (3) HbA1c ≥ 6.5% within 3 months prior to surgery; and (4) Fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) on two separate occasions during the preoperative evaluation.

Primary and secondary outcome measures

There were three primary outcomes. First, length of hospital stay was defined as the number of days from the date of surgery to the date of discharge. Second, postoperative complications were assessed using the Clavien-Dindo classification system[13], which is a standardized method for grading surgical complications based on the type of treatment required to correct the complication. Complications of grade II or higher were considered significant, which helps standardize the reporting of surgical outcomes and allows for meaningful comparisons across different studies. Third, the 30-day readmission rate was defined as any unplanned readmission to the hospital within 30 days of discharge.

The secondary outcome of QOL was assessed using the European Organization for Research and Treatment of Cancer QOL Questionnaire (EORTC QLQ-C30) and gastric cancer-specific module (QLQ-STO22)[14-16].

Statistical analyses

All statistical analyses were performed using R-software, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-sided *P*-value of < 0.05.

Continuous variables are presented as mean ± SD or median with interquartile range (IQR), depending on the distribution of data. Categorical variables are expressed as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test and visual inspection of the Q-Q plots.

To minimize the impact of potential confounding factors, we employed propensity score matching. The propensity score was calculated using a logistic regression model that included the following variables: Age, sex, BMI, smoking status, alcohol consumption, comorbidities, tumor stage, and type of gastrectomy. Diabetic and non-diabetic patients were matched 1: 1 using the nearest neighbor method with a caliper width of 0.2 SDs of the logit of the propensity score. The balance of covariates before and after matching was assessed using standardized mean differences, with a value < 0.1 considered indicative of good balance.

For the matched cohort, continuous outcomes were compared using paired *t*-tests or Wilcoxon signed-rank tests as appropriate. McNemar's test was used to assess categorical outcomes. The length of hospital stay was also analyzed using a linear regression model, adjusting for potential residual confounders. Postoperative complications were compared using logistic regression and the results were presented as ORs with 95%CIs. The 30-day readmission rates were analyzed using the Cox proportional hazards model, and the results were expressed as HRs with 95%CIs.

QOL scores were compared between diabetic and non-diabetic patients using linear mixed-effects models to account for repeated measurements over time. The models included fixed effects for diabetes status, time point, and their interaction as well as random effects for patients.

Sample size calculation

Based on previous studies, we estimated that the presence of diabetes is associated with a 20% increase in the length of hospital stay. Assuming an SD of 5 days in both groups, a power of 80%, and a two-sided alpha of 0.05, we calculated that

a minimum of 250 patients per group would be required to detect this difference. To account for potential exclusions and increase the power of the secondary analyses, we aimed to include at least 300 patients in each group after propensity score matching.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki, and adhered to the ethical guidelines for medical and health research involving human subjects. Patient confidentiality was maintained throughout the study and all data were de-identified prior to analysis. The study results will be reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Guidelines for cohort studies[17].

RESULTS

Patient characteristics

In total, 1427 patients underwent radical gastrectomy for gastric cancer during the study period. After applying the exclusion criteria, 1210 patients were included in the final analysis, comprising 302 patients with diabetes mellitus (25%) and 908 patients without diabetes (75%). Propensity score matching created two comparable groups of 280 patients (560 patients each) for the primary analysis.

Table 1 shows the baseline characteristics of the study population before and after propensity score matching. Before matching, diabetic patients were significantly older (mean age 68.5 ± 9.2 *vs* 63.7 ± 11.3 years, $P < 0.001$) and had a higher BMI (26.3 ± 4.1 *vs* 24.8 ± 3.7 kg/m², $P < 0.001$) compared to non-diabetic patients. They also had a higher prevalence of hypertension (62% *vs* 41%, $P < 0.001$) and cardiovascular diseases (28% *vs* 17%, $P < 0.001$). After propensity score matching, these differences were substantially reduced, with all standardized mean differences of < 0.1, indicating a good balance between the groups.

Among patients with diabetes, 267 (88.4%) had type 2 diabetes and 35 (11.6%) had type 1 diabetes. The median duration of diabetes was 8.5 years (IQR: 4.2-13.7 years). The mean HbA1c level was 7.4% ± 1.2%. Regarding diabetes management, 143 patients (47.4 %) were on oral antidiabetic medications alone, 84 (27.8%) were on insulin therapy, and 75 (24.8%) were on a combination of oral medication and insulin.

Primary outcomes

In the matched cohort, patients with diabetes had a significantly longer mean length of hospital stay compared to non-diabetic patients (12.7 ± 5.3 days *vs* 10.4 ± 4.1 days, $P < 0.001$). The mean difference was 2.3 days (95%CI: 1.7-2.9 days). After adjusting for potential residual confounders in a linear regression model, diabetes remained significantly associated with increased length of stay ($\beta = 2.1$ days, 95%CI: 1.5-2.7 days, $P < 0.001$).

Diabetic patients experienced a higher rate of overall postoperative complications (Clavien-Dindo grade II or higher) than non-diabetic patients (38.2% *vs* 26.8%, $P = 0.004$). The odds ratio for experiencing a complication in diabetic patients was 1.68 (95%CI: 1.32-2.14, $P < 0.001$) after adjusting for age, BMI, and tumor stage.

As shown in Table 2, patients with diabetes had significantly higher rates of surgical site infections (15.7% *vs* 8.9%, $P = 0.015$), pneumonia (12.5% *vs* 7.1%, $P = 0.037$), and urinary tract infections (9.3% *vs* 4.6%, $P = 0.029$). Additional complications listed in Table 2 included anastomotic leakage (6.1% *vs* 3.9%, $P = 0.241$) and deep vein thrombosis (3.2% *vs* 1.8%, $P = 0.281$), though these differences were not statistically significant.

The 30-day readmission rate was significantly higher in the diabetes group than in the non-diabetes group (12.5% *vs* 7.8%, $P = 0.020$). The HR for readmission in diabetic patients was 1.64 (95%CI: 1.18-2.28, $P = 0.003$) after adjusting for age, comorbidities, and postoperative complications.

Secondary outcomes

Analysis of the EORTC QLQ-C30 and QLQ-STO22 questionnaires revealed that diabetic patients had lower QOL than non-diabetic patients in several domains. As shown in Table 3, significant differences were observed in physical functioning (mean difference: -8.3 points, 95%CI: -11.7 to -4.9, $P < 0.001$), fatigue (+7.2 points, 95%CI: 4.1 to 10.3, $P < 0.001$), and pain (+6.5 points, 95%CI: 3.2 to 9.8, $P < 0.001$) at 3 months post-surgery. These differences persisted, albeit to a lesser extent, at 6 and 12 months postoperatively, with data presented in Table 3 showing physical functioning differences decreasing to -5.6 points (95%CI: -8.5 to -2.7, $P < 0.001$) at 12 months.

Gastric cancer-specific symptoms, as measured by the QLQ-STO22 and detailed in Table 3, showed that diabetic patients experienced more problems with reflux symptoms (+5.8 points, 95%CI: 2.7 to 8.9, $P = 0.002$) and eating restrictions (+7.1 points, 95%CI: 3.9 to 10.3, $P < 0.001$) throughout the first year after surgery. The data demonstrated that these differences remained significant at 12 months post-surgery, with eating restrictions showing a difference of +4.4 points (95%CI: 1.6 to 7.2, $P = 0.002$).

DISCUSSION

This large retrospective cohort study provides comprehensive evidence that diabetes mellitus is associated with poor outcomes in patients undergoing radical gastrectomy for gastric cancer. Our findings demonstrate that patients with diabetes experience longer hospital stays, higher rates of postoperative complications, increased 30-day readmission

Table 1 Baseline characteristics of patients before and after propensity score matching, *n* (%)

Characteristic	Before matching			After matching		
	Diabetic (*n* = 300)	Non-diabetic (*n* = 900)	*P* value	Diabetic (*n* = 280)	Non-diabetic (*n* = 280)	*P* value
Age (years)	68.5 ± 9.2	63.7 ± 11.3	< 0.001	67.8 ± 9.5	67.3 ± 10.1	0.54
Male sex	190 (62.9)	536 (59.0)	0.22	172 (61.4)	169 (60.4)	0.80
BMI (kg/m²)	26.3 ± 4.1	24.8 ± 3.7	< 0.001	25.9 ± 3.9	25.7 ± 3.8	0.53
Hypertension	187 (61.9)	372 (41.0)	< 0.001	168 (60.0)	165 (58.9)	0.79
CVD	85 (28.1)	154 (17.0)	< 0.001	75 (26.8)	72 (25.7)	0.77
Tumor stage			0.18			0.95
I	70 (23.2)	236 (26.0)		66 (23.6)	68 (24.3)	
II	93 (30.8)	300 (33.0)		89 (31.8)	87 (31.1)	
III	139 (46.0)	372 (41.0)		125 (44.6)	125 (44.6)	

BMI: Body mass index; CVD: Cardiovascular disease.

Table 2 Incidence of specific postoperative complications in diabetic and non-diabetic patients, *n* (%)

Complication	Diabetic (*n* = 280)	Non-diabetic (*n* = 280)	*P* value
Surgical site infection	44 (15.7)	25 (8.9)	0.015
Pneumonia	35 (12.5)	20 (7.1)	0.037
Urinary tract infection	26 (9.3)	13 (4.6)	0.029
Anastomotic leakage	17 (6.1)	11 (3.9)	0.241
Deep vein thrombosis	9 (3.2)	5 (1.8)	0.281

rates, reduced long-term survival, and a lower QOL than patients without diabetes.

The observed increase in the length of hospital stay (mean difference of 2.3 days) for diabetic patients was clinically significant and consistent with previous studies in other surgical populations[18,19]. This prolonged hospitalization may be attributed to several factors, including a higher incidence of postoperative complications, need for more intensive glycemic control, and management of diabetes-related comorbidities, and has significant economic impacts due to the high costs associated with inpatient care[20].

The higher rate of postoperative complications in patients with diabetes (OR, 1.68) was a critical finding in our study. The increased incidence of surgical site infections, pneumonia, and urinary tract infections in patients with diabetes is consistent with the known effects of diabetes on immune function and wound healing[21]. These complications contribute to prolonged hospital stays and may also have long-term implications for patient recovery and QOL.

The elevated 30-day readmission rate in patients with diabetes (12.5% *vs* 7.8%) is particularly concerning, as it suggests that the impact of diabetes on recovery extends beyond the initial hospital stay. This finding highlights the need for enhanced postdischarge care and close follow-up of patients with diabetes to prevent and promptly address any complications that may arise after leaving the hospital.

Analysis of the EORTC QLQ-C30 and QLQ-STO22 questionnaires revealed a dynamic pattern in QOL scores over time. While both groups showed improvements across all domains during the 12-month follow-up period, patients with diabetes consistently scored lower than non-diabetic patients. The gap was most pronounced at 3 months post-surgery, particularly in terms of physical functioning (8.3-point difference) but gradually narrowed by 12 months (5.6-point difference). This suggests that patients with diabetes may require longer recovery periods to achieve optimal functioning. Similarly, fatigue scores showed the greatest between-group difference at 3 months (7.2 points) with gradual convergence over time (4.4 points at 12 months), indicating that patients with diabetes experience more prolonged recovery-related fatigue. The persistent differences in eating restrictions and reflux symptoms (7.1 and 5.8 points respectively, at 3 months) highlight the need for targeted nutritional support and symptom management strategies in patients with diabetes.

The robustness of our findings, as demonstrated by the sensitivity analyses, strengthens the validity of our conclusions. The consistent results obtained from the unmatched cohort analysis and the stability of the findings after multiple imputations for missing data support the reliability of our primary analysis.

This study has several strengths, including its large sample size, use of propensity score matching to minimize confounding factors, and comprehensive assessment of both short- and long-term outcomes. The inclusion of QOL measures provides a patient-centered perspective that is often lacking in similar studies.

Table 3 Mean quality of life scores at 3, 6, and 12 months following surgery, mean ± SD

Domain	Time point	Diabetic	Non-diabetic	Mean difference (95%CI)	*P* value
Physical functioning	3 months	65.2 ± 18.7	73.5 ± 16.9	-8.3 (-11.7 to -4.9)	< 0.001
	6 months	71.8 ± 17.3	78.9 ± 15.6	-7.1 (-10.2 to -4.0)	< 0.001
	12 months	75.6 ± 16.1	81.2 ± 14.8	-5.6 (-8.5 to -2.7)	< 0.001
Fatigue	3 months	43.7 ± 22.4	36.5 ± 20.1	7.2 (4.1 to 10.3)	< 0.001
	6 months	38.9 ± 20.8	33.1 ± 18.7	5.8 (2.9 to 8.7)	< 0.001
	12 months	35.2 ± 19.5	30.8 ± 17.9	4.4 (1.7 to 7.1)	0.002
Pain	3 months	32.8 ± 24.6	26.3 ± 22.1	6.5 (3.2 to 9.8)	< 0.001
	6 months	28.5 ± 22.9	23.7 ± 20.8	4.8 (1.7 to 7.9)	0.003
	12 months	25.1 ± 21.3	21.4 ± 19.5	3.7 (0.8 to 6.6)	0.013
Reflux symptoms	3 months	26.9 ± 22.7	21.1 ± 19.8	5.8 (2.7 to 8.9)	0.002
	6 months	24.3 ± 21.1	19.8 ± 18.5	4.5 (1.6 to 7.4)	0.004
	12 months	22.7 ± 20.3	18.9 ± 17.9	3.8 (1.1 to 6.5)	0.006
Eating restrictions	3 months	38.6 ± 24.9	31.5 ± 22.3	7.1 (3.9 to 10.3)	< 0.001
	6 months	34.2 ± 23.1	28.7 ± 20.8	5.5 (2.5 to 8.5)	< 0.001
	12 months	31.3 ± 21.7	26.9 ± 19.5	4.4 (1.6 to 7.2)	0.002

Higher scores indicate better physical functioning and worse symptoms/problems in other domains.

However, this study has some limitations. First, the retrospective nature of the study introduces the potential for unmeasured confounding, although our E-value calculations suggest that any unmeasured confounder would need to have a substantial effect on negating our findings. Second, the single-center design may have limited the generalizability of our results to other healthcare settings and populations. Third, although we adjusted for HbA1c levels, we did not have detailed data on the quality of glycemic control throughout the perioperative period, which may have provided additional insights into the mechanisms underlying the observed associations.

CONCLUSION

This study provides robust evidence that diabetes mellitus is associated with poor short- and long-term outcomes in patients undergoing radical gastrectomy for gastric cancer. These findings have several important clinical implications and should inform the perioperative care protocols for patients with diabetes who undergo radical gastrectomy. First, preoperative optimization of glycemic control should be prioritized with consideration of endocrinology consultations for patients with HbA1c > 7.5%. Second, implementing enhanced recovery after surgery protocols specifically modified for patients with diabetes may help mitigate complications. Such protocols should include strict glycemic control (target range 140-180 mg/dL), early mobilization to prevent muscle deconditioning, specialized wound care protocols, and prophylactic measures against common infections. Third, given the high readmission rates, establishing a structured follow-up program with regular monitoring of glycemic control and early detection of complications is crucial. Finally, persistent QOL impairments suggest the need for extended rehabilitation support and nutritional counseling, particularly focusing on managing eating restrictions and reflux symptoms. By addressing the specific needs of this high-risk population, we may improve not only immediate postoperative outcomes but also long-term survival and QOL in diabetic patients with gastric cancer.

FOOTNOTES

Author contributions: Zhao L designed this study; Wei L contributed to data collection, and Zhao L and Wei L jointly drafted the initial draft and formal analysis; Fei XL provided guidance and contributed to the methodology and visualization of this study. Zhao L, Wei L, and Fei XL jointly validated the study and edited the entire content of the manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic full-thickness resection *vs* surgical resection for gastric stromal tumors: Efficacy and safety using propensity score matching

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Abstract

BACKGROUND

Endoscopic full-thickness resection (EFTR) is increasingly used for treating gastrointestinal stromal tumors (GISTs) in the stomach.

AIM

To compare the efficacy, tolerability, and clinical outcomes of EFTR *vs* surgical resection (SR) for gastric GISTs.

METHODS

We collected clinical data from patients diagnosed with GISTs who underwent either EFTR or SR at our hospital from October 2011 to July 2024. Patients were matched in a 1:1 ratio based on baseline characteristics and tumor clinical-pathological features using propensity score matching. We analyzed perioperative outcomes and follow-up data. The primary outcome measure was progression-free survival (PFS).

RESULTS

Out of 912 patients, 573 met the inclusion criteria. After matching, each group included 95 patients. The EFTR group demonstrated statistically significant advantages over the SR group in average operative time ($P < 0.001$), length of hospital stay ($P < 0.001$), time to resume liquid diet ($P < 0.001$), incidence of adverse events ($P = 0.031$), and hospitalization costs ($P < 0.001$). The *en bloc* resection rate

was significantly different, with SR group at 100% and EFTR group at 93.7% (P = 0.038). The median follow-up was 2451.50 days. Recurrence occurred in 3 patients in the EFTR group and 4 patients in the SR group, with no statistically significant difference (P = 1.000). Factors associated with PFS included age, tumor size, high-risk category in the modified National Institutes of Health (NIH) risk score, and resection status. Resection status was identified as an independent prognostic factor for PFS (P = 0.0173, hazard ratios = 0.0179, 95%CI: 0.000655-0.491). Notably, there was no statistically significant difference in PFS between the two groups.

CONCLUSION

This study is a non-inferiority design. The EFTR group significantly outperformed the SR group in terms of operative time, length of hospital stay, time to resume a liquid diet, incidence of adverse events, and hospitalization costs, demonstrating its higher economic efficiency and better tolerability. Additionally, although the *en bloc* resection rate was lower in the EFTR group compared to the SR group, there were no significant differences in tumor recurrence rates and progression-free survival between the two groups. This study found no statistical difference in the primary endpoint of postoperative recurrence rates between the two groups. However, due to sample size limitations, this result requires further validation in larger-scale studies. The current results should be viewed as exploratory evidence.

Key Words: Endoscopic full-thickness resection; Gastrointestinal stromal tumors; Surgical resection; Propensity score matching; Efficacy; Progression-free survival

Core Tip: This study evaluates endoscopic full-thickness resection (EFTR) *vs* surgical resection (SR) for gastric gastrointestinal stromal tumors. EFTR shows significant advantages in operative time, hospital stay, and adverse events compared to SR, with improved economic efficiency and tolerability. Although EFTR has a lower *en bloc* resection rate, both treatments yield similar tumor recurrence rates and progression-free survival. This research highlights EFTR's potential benefits in clinical practice while emphasizing that both methods offer comparable long-term outcomes.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common malignant mesenchymal tumors, primarily occurring in the stomach (50.0%-60.0%) and small intestine (30.0%-35.0%), with a smaller percentage in the colon and rectum (5.0%) and very rarely in the esophagus (< 1.0%)[1,2]. GISTs vary widely in clinical behavior, ranging from tumors with minimal metastatic potential to malignant and life-threatening diseases. One of the most notable features of GISTs is their unpredictable and variable behavior[3-5]. Endoscopic ultrasonography (EUS) is the preferred method for evaluating uncertain GISTs and/or tissues that cannot be diagnosed through biopsy. EUS can differentiate tumor size, invasion depth, and growth patterns, providing guidance for the diagnosis and treatment of GISTs[6,7].

Although GIST management principles have been standardized in various international guidelines, there remains significant controversy, particularly in dealing with smaller-sized GISTs (< 5 cm). According to recommendations from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), for small gastric subepithelial lesions (SELs) < 2 cm and without malignant features, monitoring with EUS is sufficient without the need for histopathological examination. For primary, localized gastric GISTs larger than 2 cm, surgical resection (SR) is recommended. Additionally, SELs that present with ulceration, bleeding, or symptoms should be considered for resection[2,8]. However, research by Kobayashi *et al*[9] indicates that since EUS measurements are typically 0.5 cm smaller than pathological tumor diameters, even for gastric GISTs < 2 cm and without malignant features, further examination such as EUS-guided fine-needle aspiration (FNA) should be considered. Multiple factors need to be considered in the assessment and management of GISTs, particularly when choosing a resection approach, and no consensus has yet been reached.

GISTs have potential malignant characteristics, with hematogenous metastasis being the primary mode of spread, and lymph node metastasis being rare. Therefore, lymph node dissection is not necessary during SR. In recent years, based on endoscopic submucosal techniques and with the development of reliable endoscopic closure technologies and tools, endoscopic full-thickness resection (EFTR) is emerging as an option for treating subepithelial tumors and epithelial lesions with significant fibrosis[10-12]. In a 2023 retrospective study by Shichijo *et al*[13] from Japan, it was found that

EFTR is effective for treating gastric submucosal tumors (SMTs) ranging from 11 to 30 mm[13]. EFTR is primarily suited for submucosal GISTs that grow into the serosal layer. If endoscopic submucosal dissection (ESD) reveals tight adhesion to the serosal layer, EFTR can be considered. EFTR can be categorized into "exposed" and "non-exposed" types. In exposed EFTR, full-thickness resection is performed using tunnel or non-tunnel techniques, followed by defect closure. In non-exposed EFTR, resection is done safely between the serosa and serosa before isolating the lesion[14]. However, EFTR encounters three primary challenges: Restricted insufflation and visibility within the cavity, limited operational space, and insufficient exposure of the resection margins[15,16]. EFTR has certain limitations, such as cases involving GISTs located in the small intestine or retroperitoneum, which are often beyond the reach of endoscopy. Since endoscopic treatment requires a clear view within the gastrointestinal tract, some GISTs that cause bleeding or obstruction are not ideal candidates for endoscopic treatment. EFTR demands complex endoscopic techniques, including electrocautery, hemostasis, and endoscopic closure of gastrointestinal defects[17-20]. Additionally, the procedure involves creating an artificial pneumoperitoneum, which may lead to complications such as pleural or peritoneal fistulas, potentially resulting in serious infections. Thus, EFTR currently faces challenges related to standardization and broader implementation[11,21,22]. Ensuring *en bloc* resection and managing potential recurrence risks remain ongoing concerns for clinicians. There is still some debate regarding the long-term efficacy of EFTR in treating GISTs[23,24]. Many studies on EFTR for gastric GISTs have demonstrated its short-term safety. However, further clinical research and long-term follow-up are needed to assess postoperative recurrence rates, long-term survival, and patient quality of life. Previous research often shows a significant imbalance, with larger numbers of patients and larger tumor sizes in the SR group compared to the EFTR group, leading to considerable selection bias. In this study, we used propensity score matching (PSM) to create comparable cohorts and evaluate the safety and efficacy of EFTR *vs* SR for GISTs.

MATERIALS AND METHODS

Study subjects

A retrospective collection of 912 patients with primary gastric GIST who received EFTR or SR at Shengjing Hospital, China Medical University, from November 2011 to July 2023. After applying inclusion and exclusion criteria, 573 patients were ultimately selected for further analysis (Figure 1).

Inclusion criteria: (1) Age > 18 years; (2) Preoperative EUS confirming a gastric tumor originating from the muscularis propria; (3) No evidence of GIST recurrence or metastasis before treatment; (4) Underwent EFTR or SR; and (5) Postoperative pathological diagnosis of GIST.

Exclusion criteria: (1) Coexisting malignant tumors; (2) Severe heart, liver, or kidney dysfunction; (3) Incomplete treatment or lack of complete medical records; (4) Mental illness or cognitive impairment that prevents cooperation with the study; (5) Tumor size > 5 cm or already metastasized; or (6) Tumor located in parts of the digestive system other than the stomach.

EFTR and surgical procedures for gastric GIST were performed by experienced specialists and met the relevant surgical quality control standards. All patients underwent necessary examinations to exclude contraindications for endoscopic or surgical treatment, discontinued anticoagulants for more than one week, and fasted for more than 6 hours preoperatively. All patients were informed about the benefits and risks of the surgery, signed an informed consent form, and were admitted for treatment. Postoperatively, patients were closely monitored for vital signs. Depending on the condition, they were fasted for 24-72 hours, and received routine treatments such as fluid supplementation, proton pump inhibitors (PPI), and antibiotics, with gastrointestinal decompression if necessary. Depending on abdominal signs, patients were started on liquid diet on postoperative day 2-4. If patients experienced no discomfort after resuming diet and had normal temperature and laboratory tests, they could be discharged. After discharge, they continued oral PPI for 1 month. Follow-up was conducted 3 months postoperatively with endoscopy, and subsequently once a year or until death, including endoscopy, abdominal ultrasound, or computed tomography scans, to monitor wound healing, local recurrence, and metastasis.

The study design adheres to the Helsinki Declaration. All relevant procedures have been approved by the Institutional Review Board and Ethics Committee of China Medical University and have completed clinical registration, with the registration number 2024PS877K.

Data collection

Baseline and pathological clinical characteristics of enrolled patients were collected from the HIS system of Shengjing Hospital, China Medical University, including gender, age, tumor location, tumor size, growth pattern, operation time, surgical method, margin status, modified National Institutes of Health (NIH) risk score, occurrence of adverse events, time to recovery of liquid diet post-surgery, and hospital stay duration. The primary outcome was progression-free survival (PFS), defined as the interval between the tumor resection date and confirmed disease progression or death. Patients were reviewed at the final follow-up date if none of the aforementioned events had occurred.

EFTR and SR

EFTR group: The patient is positioned in either the left lateral or supine position, and the surgery is performed under endotracheal intubation and general anesthesia. CO_2 is used as the insufflation gas throughout the procedure. A triangular knife is used to dissect the mucosal layer at the edge of the lesion, and an IT knife is used to perform full-

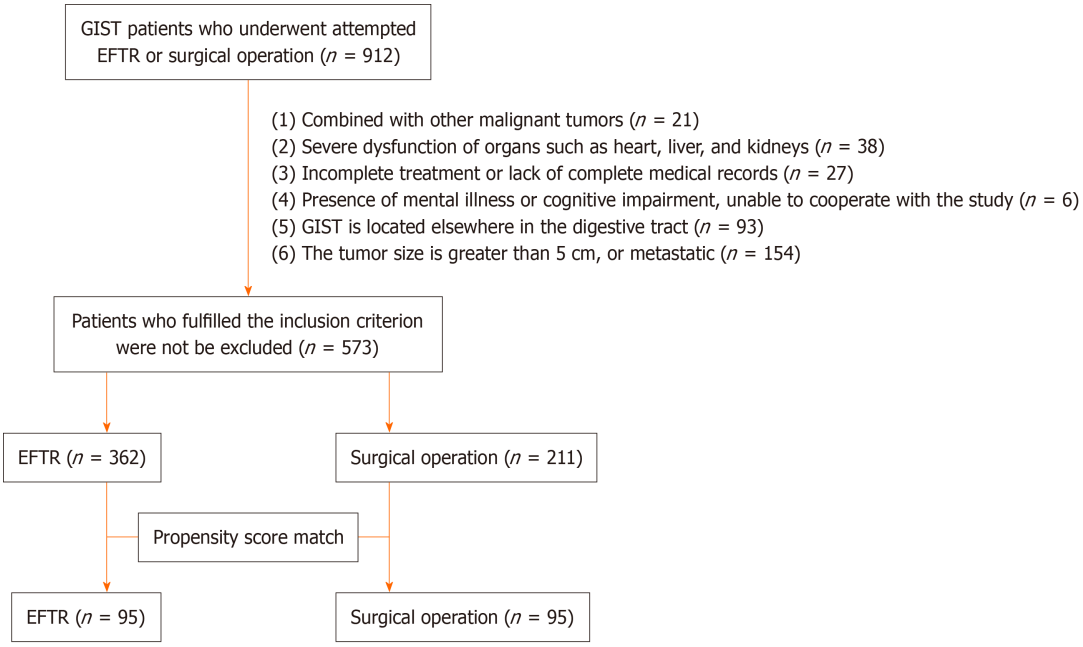

Figure 1 Flow diagram of the study. GIST: Gastrointestinal stromal tumor; EFTR: Endoscopic full-thickness resection.

thickness resection of the tumor and surrounding tissue, including the mucosa, submucosa, muscularis, and serosa. During resection, care is taken to protect the adjacent tissue of the gastric wall and the tumor capsule. Hemostasis is achieved using a thermal hemostatic clamp during the procedure. If significant pneumoperitoneum is observed intraoperatively, a puncture at the McBurney's point can be performed to release gas. The TTSC or OTSC system is used to close the wound. The resected tissue is retrieved using an endoscopic grasper and sent for pathological examination (Figure 2).

SR group: Based on tumor location and growth pattern assessed by the senior physician, an appropriate surgical method is chosen. Laparoscopic wedge resection with a linear stapler is the primary method for treating GISTs, while tumors adhering closely to surrounding tissues or vital organs and blood vessels are treated with open surgery. All EFTRs and surgical procedures are performed by qualified and experienced specialists. Postoperative pathological diagnosis for intermediate to high-risk patients, according to the modified NIH risk score, is supplemented with imatinib targeted therapy.

Statistical analysis

Data analysis and graphing were performed using SPSS 27.0 (IBM SPSS Statistics, Armonk, NY, United States: IBM Corp) and R 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Univariate analysis of variance was used to explore factors influencing operative time. Multivariate logistic regression analysis was conducted to investigate factors affecting adverse events. All statistical tests were two-sided with a significance level of $\alpha = 0.05$; differences were considered statistically significant if $P < 0.05$. Survival analysis was performed using the Kaplan-Meier method and Log-Rank test to assess differences in survival time. The Cox proportional hazards model was used for univariate and multivariate analysis. Variables with $P < 0.1$ from univariate analysis were included in the multivariate analysis to identify independent prognostic factors. Hazard ratios (HR) and their 95%CI were calculated.

PSM

Propensity scores were calculated using logistic regression analysis. In the PSM analysis, a caliper width of 0.2 was used to match the EFTR group with the surgical group. A 1:1 PSM ratio was employed, using the nearest neighbor matching method to minimize differences in age, gender, tumor location, tumor size, modified NIH risk score, and tumor growth type. The standardized mean difference (SMD) was used to test the average distribution of baseline characteristics between groups, with an overall SMD < 0.1 indicating good balance. Figure 3 illustrates the results of the PSM.

RESULTS

Patient characteristics

After PSM, each group (EFTR and SR) included 95 patients. In the matched cohort, there were differences in sex ($P = 0.124$), tumor location ($P < 0.001$), tumor size ($P < 0.001$), modified NIH risk score ($P < 0.001$), and tumor growth type ($P = 0.103$). After PSM, the two groups were well balanced in all variables except age (Table 1).

Table 1 Baseline characteristics of the patients, *n* (%)

Variables	Pre-matched corhort				Matched corhort			
	EFTR, *n* = 362	SR, *n* = 211	*P* value	SMD	EFTR, *n* = 95	SR, *n* = 95	*P* value	SMD
Age (years), mean ± SD	58.98 ± 8.14	59.07 ± 10.61	0.906	0.010	59.79 ± 8.90	58.64 ± 9.13	0.328	0.127
Sex			0.124	0.140			1.000	< 0.001
Males	123 (34.0)	86 (40.8)			37 (38.9)	37 (38.9)		
Females	239 (66.0)	125 (59.2)			58 (61.1)	58 (61.1)		
Tumor location			< 0.001	0.743			0.946	0.088
Cardia	21 (5.8)	5 (2.4)			4 (4.2)	3 (3.2)		
Fundus	208 (57.5)	60 (28.4)			36 (37.9)	37 (38.9)		
Body	113 (31.2)	100 (47.4)			44 (46.3)	42 (44.2)		
Antrum	20 (5.5)	46 (21.8)			11 (11.6)	13 (13.7)		
Growth pattern			0.103	0.148			0.746	0.070
Endophytic	276 (76.2)	147 (69.7)			70 (73.7)	67 (70.5)		
Exophytic	86 (23.8)	64 (30.3)			25 (26.3)	28 (29.5)		
Tumor size (cm), mean ± SD	1.73 ± 0.84	3.08 ± 1.11	< 0.001	1.371	2.57 ± 11.1	2.62 ± 1.15	0.763	0.044
Modified NIH score			< 0.001	1.450			0.950	0.086
Very low risk	284 (78.5)	42 (19.9)			32 (33.7)	34 (35.8)		
Low risk	70 (19.3)	141 (66.8)			55 (57.9)	53 (55.8)		
Intermediate risk	5 (1.4)	18 (8.5)			5 (5.3)	4 (4.2)		
High risk	3 (0.8)	10 (4.7)			3 (3.2)	4 (4.2)		

EFTR: Endoscopic full-thickness resection; SR: Surgical resection; SMD: Standardized mean difference; NIH: National Institutes of Health.

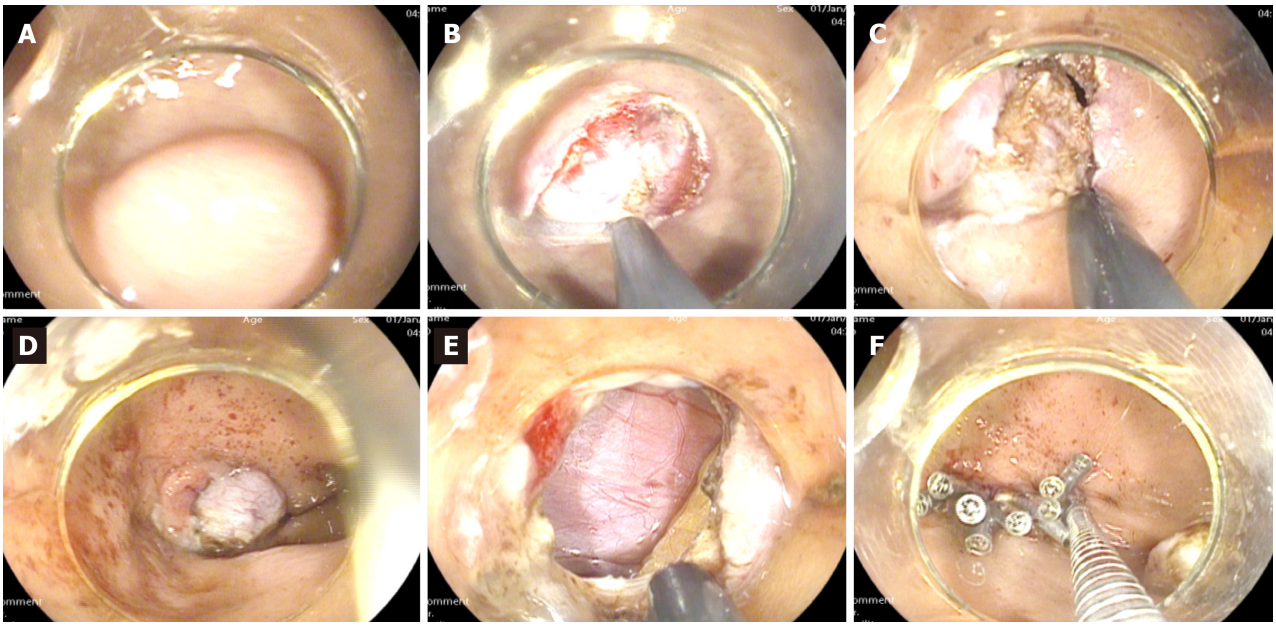

Figure 2 Intraoperative images of endoscopic full-thickness resection. A: White light observation, locating the submucosal tumor; B: Incision of the tumor's superficial mucosa; C: Layer-by-layer dissection, timely electrocoagulation for hemostasis; D: Complete exposure of the tumor; E: Tumor resection, with full-thickness gastric wall resection visible; F: Closure of the wound using a metal clip.

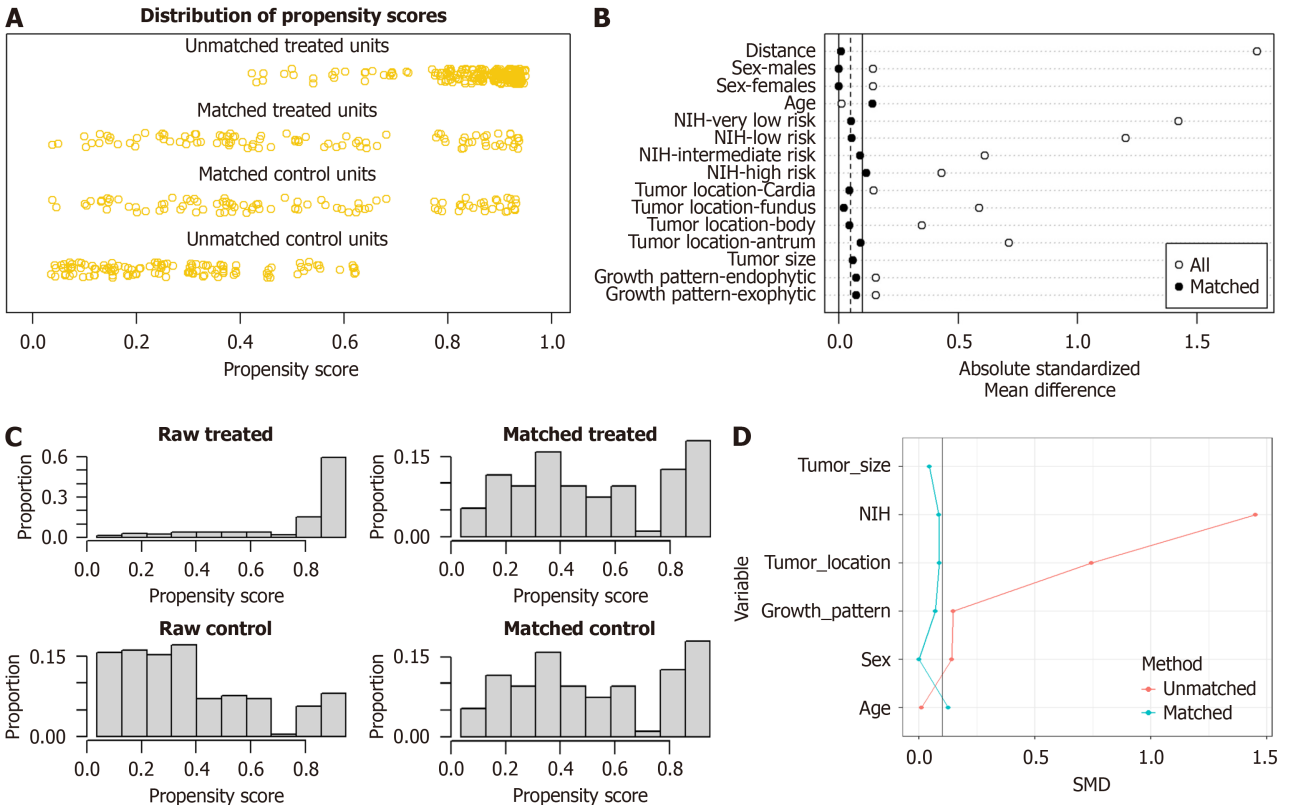

Figure 3 Data balance before and after propensity score matching. A: Jitter plot of cohort before and after propensity score matching (PSM); B: Standardized mean difference before and after PSM; C: Histogram of propensity scores; D: Line plot of individual differences before and after PSM. SMD: Standardized mean difference.

Short-term outcomes comparison

Comparing perioperative conditions (Table 2), the EFTR group had an average surgery time of 91.21 minutes, significantly shorter than the SR group's 123.11 minutes ($P < 0.001$). The EFTR group also returned to liquid diet in an average of 3.43 days, compared to 7.43 days for the SR group ($P < 0.001$). The EFTR group had an average hospital stay of 8.39 days, significantly shorter than the SR group's 16.32 days ($P < 0.001$). However, the SR group had a 100% *en bloc* resection rate, while the EFTR group had 93.7% ($P = 0.038$). Adverse event rates were significantly lower in the EFTR group (22.1% *vs* 40.0%, $P = 0.031$). Postoperative fever was transient and mild for both groups. Infections and peritonitis were managed effectively in both groups, with similar outcomes. The EFTR group incurred lower average hospital costs [30734.22 China yuan (CNY)] compared to the SR group (53231.56 CNY) ($P < 0.05$; Table 2).

Long-term prognosis

In this study, the matched cohort was followed with a median follow-up time of 2451.50 days (interquartile range: 1216.00-3464.45). The overall PSF rates at 1 year, 3 years, 5 years, and 10 years were 99.45%, 98.86%, 98.09%, and 94.01%, respectively. Prior to the last follow-up, 4 patients in the EFTR group and 3 patients in the SR group experienced tumor recurrence, with no statistically significant difference between the two groups ($P = 0.37$) according to Kaplan-Meier survival analysis (Figure 4).

Further analysis using the Cox proportional hazards model revealed several prognostic factors for PSF. Univariate Cox regression analysis identified age ($P = 0.0621$), tumor size ($P = 0.0937$), high-risk status in the modified NIH risk score ($P = 0.0273$), and resection status ($P = 0.0104$) as prognostic factors. Multivariate Cox regression analysis confirmed that resection status was an independent prognostic factor ($P = 0.0173$, HR = 0.0179, 95%CI: 0.000655-0.491; Table 3).

DISCUSSION

The latest 2020 World Health Organization guidelines classify all GISTs as malignant, regardless of size, origin, or mitotic index[25]. The most recent guidelines from the NCCN, American Society for Gastrointestinal Endoscopy (ASGE), ESMO, and the Japanese Society of Medical Oncology recommend resection for GISTs larger than 2 cm, but there is no consensus on treating GISTs 2 cm or smaller[2,14,26,27]. NCCN guidelines suggest surgical removal for high-risk GISTs, while small GISTs (≤ 2 cm) with no malignant signs should be monitored with endoscopy or imaging. European and Japanese guidelines advocate for resection of GISTs of any size. According to ASGE standards, GISTs smaller than 2 cm and asymptomatic generally do not require treatment; instead, regular endoscopic surveillance is recommended. If necessary,

Table 2 Perioperative characteristics and long-term outcomes, *n* (%)

Variables	EFTR, *n* = 95	SR, *n* = 95	*P* value
Operation time (minute), mean ± SD	91.21 ± 57.21	123.11 ± 49.03	< 0.001
Days to resume liquid diet (day), mean ± SD	3.43 ± 1.61	7.43 ± 7.44	< 0.001
Days of hospital stay (day), mean ± SD	8.39 ± 4.40	16.32 ± 8.10	< 0.001
Adverse events			0.031
Postoperative fever	5 (5.3)	13 (13.7)	
Infection	13 (13.7)	21 (22.1)	
Peritonitis	3 (3.2)	2 (2.1)	
Bleeding	0 (0.0)	2 (2.1)	
Resection status			0.038
En bloc	89 (93.7)	95 (100.0)	
Piecemeal	6 (6.3)	0 (0.0)	
Recurrence	4 (4.2)	3 (3.2)	1.000
Hospitalization expenses (CNY), mean ± SD	30734.22 ± 15741.46	53231.56 ± 24235.56	< 0.001

EFTR: Endoscopic full-thickness resection; SR: Surgical resection; CNY: China yuan; SMD: Standardized mean difference; NIH: National Institutes of Health.

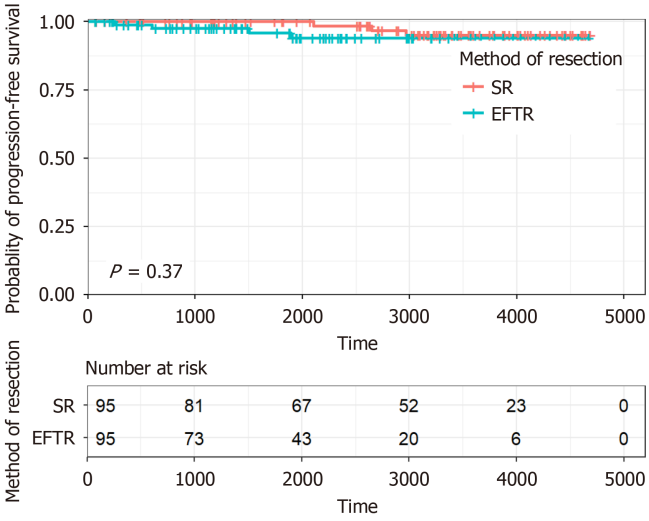

Figure 4 Kaplan-Meier survival analysis of progression-free survival. SR: Surgical resection; EFTR: Endoscopic full-thickness resection.

EUS-FNA or fine-needle biopsy can be performed for diagnosis. Based on pathological results, follow-up or surgical treatment can be chosen[9,14,28]. However, this standard has faced controversy and skepticism among many gastroenterologists in China. Given the large patient population and varying compliance in China, some patients' excessive anxiety could lead to delays in treatment, repeated endoscopic procedures, and other issues. Additionally, preoperative biopsy may increase surgical difficulty and risks such as mucosal damage, submucosal adhesion, bleeding, infection, and tumor rupture. Therefore, the 2018 consensus on GIST endoscopic diagnosis and treatment in China concludes that preoperative biopsy may not be necessary[29].

Traditional methods for GIST resection often involve open or laparoscopic surgery, which typically require large surgical sites, come with high surgical risks, longer recovery times, and higher costs[30]. With the advancement of endoscopy, endoscopic treatment offers unique advantages and is more readily accepted by patients[28]. Preoperative EUS can clarify the tumor's origin layer, size, and growth pattern, which helps in the precise selection of endoscopic treatment methods. This approach ensures the safety and effectiveness of the procedure while reducing the risk of complications[31]. Traditional endoscopic methods for GIST resection include endoscopic mucosal resection, ESD, endoscopic submucosal excavation, and EFTR[32]. EFTR can achieve complete removal of the lesion by creating a deliberate perforation, provided that the tumor remains within an intact capsule. This method offers higher resection efficiency compared to ESD[33]. The key to EFTR surgery is successfully closing the defect after resection to prevent

Table 3 Data regarding the Cox proportional hazards model

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (years)	0.921 (0.846-1.00)	0.0621	0.930 (0.848-1.02)	0.126
Sex				
Males	Reference			
Females	1.40 (0.312-6.25)	0.661		
Growth pattern				
Endophytic	Reference			
Exophytic	7.15 (1.38-36.9)	0.0189		
Tumor size (cm)	1.74 (0.910-3.33)	0.0937	2.46 (0.812-7.43)	0.112
Modified NIH score				
Very low risk	Reference		Reference	
Low risk	1.91 (0.198-18.34)	0.576	0.268 (0.00917-7.82)	0.444
Intermediate risk	7.71 (0.482-123.38)	0.149	0.463 (0.00730-29.4)	0.716
High risk	14.99 (1.35-165.33)	0.0273	1.20 (0.0239-60.2)	0.928
Resection status				
En bloc	0.0563 (0.00624-0.508)	0.0104	0.0179 (0.000655-0.491)	0.0173
Piecemeal	Reference		Reference	
Resection method				
SR	Reference			
EFTR	1.97 (0.434-8.93)	0.38		

EFTR: Endoscopic full-thickness resection; SR: Surgical resection; NIH: National Institutes of Health; HR: Hazard ratios.

peritonitis and the need for additional surgical interventions[34-36].

Shichijo *et al*[13] found through follow-up of 46 patients that EFTR is effective for treating gastric SMTs (G-SMT) ranging from 1.1 to 3.0 cm. Li *et al*[29] demonstrated through an analysis of 73 cases that endoscopic resection is safe and feasible for treating G-SMT with a diameter of less than 3 cm. In recent years, several studies have compared the efficacy of EFTR with SR for treating GISTs, but most of these studies did not perform baseline characteristic matching for the cohorts[30,37-39]. This may introduce selection bias, making endoscopic resection appear more advantageous.

In recent years, researchers have increasingly recognized that imbalances in baseline characteristics can introduce bias into study results. To mitigate this bias, a domestic study employed PSM to adjust for differences in baseline characteristics between the endoscopic and laparoscopic groups. The results indicate that, after matching, for tumors with a diameter of 2-5 cm, the endoscopic group experienced significantly higher rates of complications and longer postoperative hospital stays compared to the laparoscopic group, with these differences being statistically significant (P < 0.001)[40]. In contrast, another study utilizing PSM to compare EFTR and SR for G-SMT originating from the intrinsic muscularis propria concluded that the postoperative clinical outcomes of the two surgical approaches are comparable[41].

This study aims to compare the short-term and long-term effects of EFTR *vs* traditional SR for treating GIST after balancing patient baseline characteristics using PSM. The results indicate that the EFTR group shows significant advantages in short-term outcomes compared to the traditional surgical group, but there is little difference in long-term prognosis between the two groups. The EFTR group also demonstrates notable advantages in terms of operative time, postoperative recovery, length of hospital stay, and hospitalization costs compared to the traditional surgical group. The EFTR group had a significantly shorter operative time (91.21 minutes *vs* 123.11 minutes, P < 0.001), a notably reduced time from fasting to resuming a liquid diet (3.43 days *vs* 7.43 days, P < 0.001), and a substantially shorter hospital stay (8.39 days *vs* 16.32 days, P < 0.001). These results align with current understanding of EFTR technology, which, as a minimally invasive procedure, can reduce postoperative recovery time and hospital costs. In contrast, although traditional surgery showed a higher *en bloc* resection rate (100% *vs* 93.7%, P = 0.038), the EFTR group had a lower incidence of adverse events (22.1% *vs* 40.0%, P = 0.031), suggesting that EFTR may offer better safety and a lower complication rate.

In terms of long-term prognosis, the PFS rate was similar between the two groups (P = 0.38), and there was no significant difference in recurrence rates between the EFTR and traditional surgery groups (P = 1.0), indicating that EFTR is not inferior to traditional surgery in long-term tumor control and survival. COX regression analysis revealed that resection status is an independent prognostic factor for PFS (P = 0.0173, HR = 0.0179, 95%C: 0.000655-0.491), highlighting

the importance of *en bloc* resection. Differences in resection status may be related to the surgical approach, and while EFTR may compromise resection quality, it can still offer similar long-term survival outcomes with meticulous surgical technique and postoperative management.

This study underscores the potential advantages of EFTR in reducing postoperative recovery time and hospital expenses, while demonstrating comparable long-term outcomes to traditional surgery. Although EFTR slightly lags in *en bloc* resection rates, its benefits in postoperative recovery and economic burden make it a promising treatment option.

Future research should further explore the indications for different types of GISTs to validate long-term outcomes and optimize surgical strategies. The limitations of this study include its retrospective design and sample size constraints. Although propensity matching reduced inter-group differences, large-scale prospective randomized controlled trials are needed to confirm these findings. Future studies could investigate the long-term effects and indications of EFTR, considering the impact of technological advancements on surgical outcomes. Additionally, large-scale, multicenter clinical trials will help validate these results and provide clearer guidance for clinical practice.

CONCLUSION

For GISTs ≤ 5 cm, EFTR offers significant advantages in short-term outcomes compared to traditional surgery. Resection status is an independent prognostic factor affecting PFS, highlighting the importance of *en bloc* resection. This study is a non-inferiority design. This study found no statistical difference in the primary endpoint of postoperative recurrence rates between the two groups. However, due to sample size limitations, this result requires further validation in larger-scale studies. The current results should be viewed as exploratory evidence.

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FOOTNOTES

Author contributions: Zhao SQ, Sun SY and Wang S conceptualized and designed the research; Sun SY and Wang S screened patients and acquired clinical data; Liu X, Wang S, Guo JT, and Wang GX completed the endoscopic treatment; Zhao SQ was responsible for developing the methodology; Zhao SQ, Wang SY and Su L participated in the formal analysis and investigation; Zhao SQ wrote the original draft; Wang S, Su L and Zhao SQ participated in the review and editing; All the authors have read and approved the final manuscript. Both Sun SY and Wang S have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. This collaboration between Sun SY and Wang S is crucial for the publication of this manuscript and other manuscripts still in preparation.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Roux-en-Y jejunostomy in gastroparesis: Insight into patient perspectives and outcomes

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Abstract

BACKGROUND

Gastroparesis is a chronic motility disorder characterized by delayed gastric emptying in the absence of mechanical obstruction. Patients with refractory gastroparesis often require enteral nutrition support, but traditional feeding methods such as nasojejunal tubes and percutaneous gastrojejunostomy tubes have significant limitations including frequent displacement, infection, and impact on quality of life.

AIM

To explore patients' experience post insertion of laparoscopic Roux-en-Y jejunostomy in a cohort of eight adult patients with idiopathic gastroparesis.

METHODS

Eight patients with idiopathic gastroparesis who underwent Roux-en-Y jejunostomy placement between 2019-2022 were interviewed about their pre- and post-procedure experiences. The procedure involves creating a jejunal limb anastomosed to the proximal jejunum in a Y-configuration, with the limb brought to the abdominal wall for feeding tube insertion. This is designed to reduce leakage by diverting intestinal contents away from the stoma. Topics included symptoms, nutrition, quality of life, and comparison to previous feeding methods.

RESULTS

Post-procedure, all patients reported improvements in nausea/vomiting, and 87.5% noted reduced abdominal pain. Weight stabilized and oral intake improved in 75% of patients. Most (87.5%) described improved social confidence, increased energy, and better work/school functioning. Three patients (37.5%) eventually maintained adequate oral nutrition without jejunostomy. Minor complications

included leakage (37.5%) and hypergranulation tissue. Half the cohort used supplemental gastric venting. Most patients (87.5%) preferred Roux-en-Y jejunostomy over previous feeding tubes and would undergo the procedure again.

CONCLUSION

Despite some challenges, Roux-en-Y jejunostomy led to notable improvements in symptoms, nutrition, and quality of life for most patients with refractory gastroparesis. It may be a viable option for long-term enteral nutrition support in carefully selected patients. Further research is needed to optimize patient selection and manage complications.

Key Words: Gastroparesis; Jejunostomy; Enteral nutrition; Quality of life; Feeding tube

Core Tip: This qualitative study provides novel insights into patient experiences with Roux-en-Y jejunostomy for refractory gastroparesis. While traditional feeding tubes often have limitations, this surgical approach showed promising outcomes for symptom control and quality of life. Notable findings improvement and/or resolution of nausea/vomiting in most patients, with 37.5% eventually maintaining adequate oral nutrition without jejunostomy. The study highlights the potential of Roux-en-Y jejunostomy as a viable long-term feeding option in carefully selected patients, while also identifying ongoing challenges such as leakage and hypergranulation tissue that require proactive management.

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INTRODUCTION

Gastroparesis is a debilitating gastrointestinal disorder characterized by delayed gastric emptying in the absence of mechanical obstruction resulting in abdominal pain, nausea, vomiting, early satiety and postprandial fullness[1,2]. It can lead to malnutrition and repeated hospitalizations[3-5]. While the aetiology of gastroparesis can be attributed to various underlying diseases such as autonomic neuropathy due to diabetes, connective tissue disorders or post-surgical complications, a subset of patients present with idiopathic gastroparesis where the exact aetiology remains elusive[6]. In the absence of an identifiable cause, management of idiopathic gastroparesis can be difficult. Initial strategies include dietary modification, analgesia, use of antiemetics and prokinetics to promote gastric emptying[7,8]. If these interventions are insufficient to maintain a patient's weight, enteral nutrition may be used to ensure adequate caloric intake[9].

While various methods of enteral nutrition are available including nasogastric, nasojejunal, percutaneous endoscopic gastrostomy with a jejunal extension (percutaneous endoscopic transgastric jejunostomy), they have limitations in tolerability and quality of life impact[9,10]. Surgical jejunostomy is an alternate option but is more invasive and can be associated with complications including leakage, infection and dislodgement which has been described in other patient cohorts requiring enteral nutrition[11-13]. There has been little research exploring subjective experience post jejunostomy insertion in patients with gastroparesis.

In paediatric patients with delayed gastric emptying, Roux-en-Y jejunostomy has been shown to be an effective, safe, and well-tolerated surgical procedure for providing long-term enteral nutrition compared to other enteral feeding tubes [14]. It has been demonstrated to improve nutritional status, promote weight gain, and reduce symptoms associated with delayed gastric emptying in children[15]. There is minimal literature exploring patient experience in adults undergoing this procedure with gastroparesis. In our cohort, patients were also offered insertion of a venting gastrostomy which can be effective in managing symptoms in patients with gastroparesis[16,17]. The aim of this study is to explore patient experience post insertion of laparoscopic Roux-en-Y jejunostomy in a cohort of eight adult patients with idiopathic gastroparesis.

MATERIALS AND METHODS

Surgical technique

The procedure involves creating a jejunal limb approximately 15-40 cm distal to the ligament of Treitz, which is then anastomosed to the proximal jejunum in a Y-configuration as shown in Figure 1. This allows for the direct delivery of nutrients into the jejunum, bypassing the stomach. The Roux-en-Y anastomosis is combined with bringing the jejunal loop to the abdominal wall, where a jejunostomy feeding tube is inserted. This configuration helps to divert intestinal

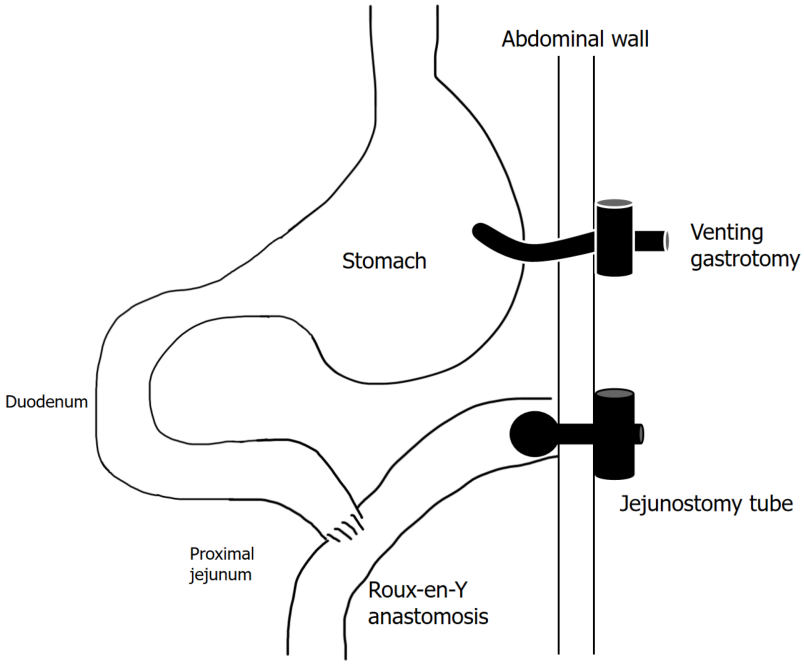

Figure 1 Roux-en-Y jejunostomy. A Roux-en-Y anastomosis with a jejunal loop brought to the abdominal wall in which the jejunostomy feeding tube is inserted. This helps to divert gastric and intestinal contents away from the stoma and reduce leakage.

contents away from the stoma and reduce leakage as well as easier tube replacement. The procedure is designed to provide long-term enteral nutrition support while minimising complications associated with other feeding tube methods. By bypassing the dysfunctional stomach in patients with delayed gastric emptying, the Roux-en-Y jejunostomy promotes improved nutrient absorption and symptom relief. The jejunostomy feeding tube allows for easy and direct access to the jejunum for feeding and medication administration. Four patients also had a venting gastrostomy inserted to allow for enhanced drainage of gastric contents minimising post prandial nausea and fullness. The decision for concurrent venting gastrostomy placement was based on: (1) Severity of pre-operative nausea/vomiting symptoms; (2) Prior response to temporary nasogastric decompression; (3) Degree of gastric retention on imaging; and (4) Patient preference after counselling regarding additional tube management requirements.

Post-operative care protocol

Patients remained nil by mouth for 24 hours post-procedure. Tube feeding was initiated at 10 mL/hour and gradually increased based on tolerance. Initial feeding regimens utilized peptide-based formula, transitioning to polymeric feeds if tolerated. Feeding rates and schedules were individualized based on symptoms and nutritional requirements. Early mobilization and oral hygiene care were emphasized. Patients received structured education on tube care, feeding techniques, and complication recognition before discharge. Regular follow-up occurred at weeks 2, 6, and 12 post-procedure, then ever 3-12 months depending on patient progress.

Study design and participants

This was a retrospective qualitative study exploring the experiences of eight patients with idiopathic gastroparesis who underwent Roux-en-Y jejunostomy placement over 2019-2022. Participants were purposely recruited from a functional gut disorder clinic based in Australia. Diagnosis was confirmed *via* gastric emptying scintigraphy demonstrating delayed gastric emptying in the absence of mechanical obstruction. The inclusion criteria were: (1) A diagnosis of idiopathic gastroparesis; (2) Having undergone Roux-en-Y jejunostomy placement between 2019 - 2022; and (3) Having had previous forms of enteral nutrition.

Statistical analysis

Patients underwent a semi-structured interview by an author (Salehi O) not involved in their care or clinical decision making to reduce risk of bias. The following topics were explored: (1) Pre-procedure symptoms and motivation for jejunostomy insertion; (2) Post-operative recovery and complications; (3) Impact on daily life including work/study, social life and sleep; (4) Weight changes and feeding regimen; (5) Comparison to prior feeding tubes; and (6) Overall experience and willingness to undergo the procedure again and/or recommend it to others. Interviews lasted 45-60 minutes and were audio-recorded with participant consent. Recordings were professionally transcribed verbatim. Thematic analysis was performed using an iterative coding process by two researchers (Salehi O, Gao WL) independently. Initial codes were compared and refined to identify key themes, with discrepancies resolved through discussion. Medical records were reviewed to verify clinical events and timelines, helping minimize recall bias. Interview questions were structured chronologically to aid accurate event recall.

RESULTS

Patients presented with severe gastroparesis symptoms and had difficulties with or failed prior enteral feeding approaches (Table 1). Nasal and throat irritation was common with nasogastric/nasojejunal tubes (7/8; 87.5%), while half had complications, including gastric perforation, leakage and infection, with gastrostomy tubes (4/8; 50%). The most frequently cited reasons for pursuing Roux-en-Y jejunostomy were to reduce social stigma and optimize nutrition (6/8; 75% each). Four patients (50%) also had a venting gastrostomy inserted. Post-procedure, patients reported improvements in nausea/vomiting (8/8; 100%) and abdominal pain (7/8; 87.5%) (Table 2). Weight stabilised and oral intake improved in 75% (6/8) of patients. Most (7/8; 87.5%) described improved social confidence, increased energy, and better work/school functioning. Specific domains showing improvement included social functioning, with reduced feeding tube visibility and increased confidence in public settings, and physical wellbeing with better symptom control and weight stabilization (Table 3). As one patient described: "Having the jejunostomy was life-changing. I could finally focus on work and socializing instead of constantly worrying about nutrition and tubes falling out".

Supplemental gastric venting was used in half the cohort (4/8; 50%). Three patients (2/8; 37.5%) were eventually able to maintain adequate nutrition *via* oral intake and had their jejunostomy tubes removed. However, one patient (1/8; 12.5%) experienced severe abdominal pain six months post-procedure, leading to jejunostomy removal. Minor leakage occurred in 3/8 (37.5%) of cases. Ongoing challenges included limitations with physical activity, managing feeding schedules around work and social activities, and sleep disruption (Table 3). Despite these challenges, most (7/8; 87.5%) patients preferred the Roux-en-Y jejunostomy over previous feeding tubes and stated they would undergo the procedure again. Overall, despite some issues, Roux-en-Y jejunostomy led to notable improvements in symptoms, nutrition and life experience for this cohort of gastroparesis patients. As one participant noted: "The recovery was difficult at times, but it was worth it. The pain and nausea are so much better now".

DISCUSSION

This case series describes patient experiences following Roux-en-Y jejunostomy placement in eight patients with refractory gastroparesis. Despite some challenges, patients generally reported positive experiences regarding symptom control, nutrition, work/study and social stigma compared to previous feeding tubes. Most patients expressed that they would undergo the procedure again. These findings suggest that Roux-en-Y jejunostomy may be a viable option for providing long-term enteral nutrition support in carefully selected gastroparesis patients. Gastroparesis is a complex disorder that profoundly impacts quality of life. Patients struggle with debilitating symptoms, malnutrition, and psychosocial distress[1]. Comorbid psychiatric conditions, such as anxiety and depression affect up to 50% of patients with gastroparesis[18,19]. While none of the patients in our series had a formal eating disorder diagnosis, restrictive eating behaviors may be observed in gastroparesis, potentially as a response to chronic symptoms[20,21]. This can further complicate management and highlights the need for multidisciplinary support.

Enteral nutrition is often required to maintain adequate nutrition in gastroparesis, but traditional feeding tubes have limitations[2]. Nasogastric and nasojejunal tubes are poorly tolerated due to nasal and throat discomfort, frequent dislodgement, and visible appearance[3]. Percutaneous endoscopic transgastric jejunostomy tubes can reduce some of these issues but are prone to retrograde migration into the stomach and may need repeat procedures for repositioning and/or replacement[22,23]. Direct surgical jejunostomy tubes provide post-pyloric access but carry risks of dehiscence, leakage, and need for regular replacement[11,24]. The Roux-en-Y jejunostomy approach may offer certain advantages in this challenging patient population. The jejunostomy tube positioning within a small bowel limb may have contributed to less dysfunction and greater longevity compared to other enteral access techniques. Importantly, patients described meaningful improvements in their day-to-day lives, with increased independence, less social stigma, and better overall functioning. While several domains showed improvement, including social functioning and physical wellbeing, patients continued to face challenges in areas such as physical activity and sleep (Table 3). Notably, three patients were able to have their jejunostomy tubes removed due to improved oral intake. This suggests the procedure may have potential to serve as a bridge to oral nutrition for certain patients, in conjunction with other gastroparesis management strategies.

The procedure was generally well tolerated. Some patients described mild leakage and pain but generally preferred the Roux-en-Y jejunostomy compared to previous feeding tubes. Half of the patients also had insertion of a venting gastrostomy to allow gastric decompression to manage symptoms. In our experience, early recognition and management of complications is crucial. For leakage, we found that careful attention to stoma care, use of barrier films/powders, and adjustment of feeding schedules/rates could help minimize impact. Hypergranulation tissue was managed with silver nitrate application and topical steroids when needed. Regular assessment of tube position and function, along with patient education on proper care techniques, helped prevent more serious complications. The concurrent use of venting gastrostomy in selected patients appeared to improve symptom control, though this requires careful consideration of the added complexity of managing two tubes.

One patient required jejunostomy tube removal six months post insertion due to persistent abdominal pain post-procedure of unclear aetiology despite extensive investigation which was unrevealing. This highlights the importance of careful patient selection and the need to consider underlying chronic pain syndromes or other comorbidities that may impact outcomes. Given the profound impact of gastroparesis on quality of life, interventions that improve patient well-being are highly significant[6]. While Roux-en-Y jejunostomy was not a perfect solution, this study suggests it can be a reasonable option for some patients struggling with other feeding tube modalities. The concurrent insertion of a venting gastrostomy may also be helpful in symptom management however the relevant risks and added burden of managing a

Table 1 Prior feeding tube experience and motivations for Roux-en-Y jejunostomy

Case	Age/sex	Previous feeding tubes	Reason (s) for procedure
1	72 males	NJT	Recurrent NJT blockage and persistent nasal/throat irritation
		Nasal/throat irritation, recurrent blockage, kinking	
		PEG	
		Recurrent infections	
2	22 females	NJT	Less social stigma as is more discrete; long term solution to maintaining weight
		Recurrent sinus infection, nasal bleeding	
		Social stigma - people constantly staring	
3	27 females	NJT	Optimise nutrition; medication administration; persistent throat/nasal irritation from NJT
		Nasal ulceration/wounds	
		Throat irritation	
		Recurrent blockage	
		Social stigma	
		PEG	
		Hypergranulation tissue	
4	18 females	NJT	Persistent nausea/vomiting; less social stigma; optimise nutrition
		Nasal/throat irritation	
		Social stigma	
5	28 females	NJT	Optimise nutrition; improve symptoms
		Recurrent "flipping"	
		Nasal/throat irritation	
		PEG	
		Dislodgement causing gastric perforation and multiple operations	
6	28 females	NJT	Persistent nausea/vomiting; optimise nutrition
		Nasal/throat irritation	
		Blockage	
		PEG	
		Leakage	
		Feeding jejunostomy	
		Leakage	
7	31 females	NJT	Optimise nutrition; less leakage and dislodgement
		Recurrent blockage	
		Dislodgement	
		PEG-J	
		Feed reflux	
		Leakage	
		Jejunal extension dislodgement	
8	26 males	NJT	Optimise nutrition; reduce leakage and pain
		Recurrent sinus infection	
		Dislodgement	
		Social stigma	

	PEG-J
	Balloon displacement
	Pain
	Leakage

PEG: Percutaneous endoscopic gastrostomy; NJT: Nasojejunal tube; PEG-J: Percutaneous endoscopic transgastric jejunostomy.

second tube need to be taken into consideration. Rigorous patient selection, preoperative counselling, and ongoing multidisciplinary support are key to optimising outcomes.

Several studies have explored patient experiences with enteral feeding tubes, providing insight into the impacts on quality of life and daily living[25-28]. Patients and caregivers describe various lifestyle disruptions with percutaneous endoscopic gastrostomy and nasal tubes including leakage and infection, disturbed sleep, limitations on activities, clothing, and social life. Patients also commonly described frustration, embarrassment, and stigma[25-28]. In our cohort, all patients had used previous feeding tubes as described in Table 1. Common issues included nasal/throat irritation, blockage, leakage and social stigma. Limited studies have explored experiences with jejunostomy tubes, particularly in adults. Cullis *et al*[15] performed a systematic review assessing whether Roux-en-Y feeding jejunostomy is a safe and effective operation in children. It was concluded that up to 50% of patients experience minor complications and the procedure can provide enteral nutrition effectively. Of note no studies analyzed in the review included patient and/or caregiver quality of life outcomes.

This study has several strengths. Firstly, our patient-centred approach provides valuable insights directly from the participants' perspectives, offering a nuanced understanding of the lived experience with Roux-en-Y jejunostomy that quantitative measures alone might not capture. The inclusion of patients with prior experience of other feeding methods allows for a comparative assessment of different enteral nutrition approaches, enhancing the context of our findings. Our evaluation encompassed multiple aspects of patient experience, including symptom control, nutrition, quality of life, and psychosocial factors, providing a holistic view of the procedure's impact. By focusing on patients with refractory gastroparesis, this study addresses an important gap in the literature for managing difficult-to-treat cases. The extended follow-up period, ranging from several months to years post-surgery, allowed us to observe not only immediate post-operative effects but also the evolving long-term impact of the procedure on patients' lives. This longitudinal perspective is particularly valuable in assessing the durability of benefits and identifying any late-onset challenges. Finally, our findings have the potential to inform clinical practice by guiding patient selection, pre-operative counselling, and post-operative management for Roux-en-Y jejunostomy in gastroparesis patients. These strengths collectively contribute to a more comprehensive understanding of this surgical intervention in the context of refractory gastroparesis management.

Based on our experience, optimal candidates for Roux-en-Y jejunostomy share several important characteristics. Primary consideration should be given to patients who have demonstrably failed conservative management and simpler feeding approaches. Candidates should demonstrate good understanding of post-operative care requirements and show motivation to participate in their ongoing care. A stable psychiatric status is essential, as the demands of managing this feeding method can be challenging. Strong social support has also proven to be a crucial factor in successful outcomes. Preoperative counselling plays a vital role in setting appropriate expectations and preparing patients for this procedure. Discussions should thoroughly cover the expected recovery timeline and help patients understand the potential need for concurrent venting gastrostomy. Emphasis should be placed on the importance of proper tube care and the management strategies for possible complications. Patients need to understand how the procedure will impact their daily activities and what long-term maintenance requirements they will need to accommodate. This comprehensive counselling approach helps ensure patients are well-prepared for both the immediate post-operative period and long-term management of their jejunostomy.

There are several important limitations in our study. The small sample size of eight patients and single-centered design limit generalizability of the findings. Patients were recruited from a specialized clinic, which may have introduced selection bias. To mitigate interviewer bias, the researcher conducting interviews was not directly involved in patient care or clinical decision-making. The small sample size of eight patients and single-centered design limit generalizability of the findings. While our results provide valuable initial insights, larger multi-center studies are needed to better understand outcomes across diverse patient populations.

However, the lack of blinding and potential for social desirability bias influencing patient responses cannot be excluded. Future studies would benefit from multiple independent interviewers and more rigorous blinding procedures. The qualitative design also inherently lacks objective outcome measures. Larger, prospective comparative studies are needed to better define the role of Roux-en-Y jejunostomy alongside other enteral access techniques for gastroparesis. Additionally, quantitative evaluation of quality of life, stigma, nutritional parameters, psychological factors and patient-reported experience metrics using validated instruments would further enrich understanding of real-world benefits *vs* risks and burden from the patient perspective.

Table 2 Post Roux-en-Y jejunostomy symptoms, nutrition and satisfaction

Case	Symptoms	Complications	Nutrition	Life impact	Venting gastrostomy	Jejunostomy in situ or removed?	Procedure again?	Follow up duration
1	Minimal nausea/vomiting Worsening abdominal pain	Persistent abdominal pain	Reduced EN frequency due to pain Minimal oral intake - could tolerate sips of clear fluids	Less social stigma - "it's great not to be stared at by strangers all the time" Mindful of heavy lifting due to strain on abdomen	No	Jejunostomy eventually removed due to persistent abdominal pain - has returned to NJT	No	2 years
2	Improved nausea and abdominal pain	Nil	Continuous EN feeds Weight stable	Less social stigma Currently studying at university	No	In situ	Yes	1 year
3	Improved nausea and abdominal pain	Leakage Hypergranulation tissue requiring multiple debridements	Able to maintain weight Overnight EN Improved oral intake	"Life changing" Has been able to travel overseas Working full time Maintaining social life Difficult to exercise due to pain	Yes	In situ	Yes	3 years
4	Improved nausea and abdominal pain	Leakage	Cyclical EN feeds initially Now able to maintain weight with oral intake	Energy levels much improved Less social stigma Currently studying at university Avoids tight fitting clothing due to leakage	Yes	Removed - able to maintain adequate oral nutrition	Yes	3 years
5	Improved nausea and abdominal pain	Cuff burst requiring jejunostomy exchange Hospital admission due to poorly controlled pain	Difficulty tolerating EN *via* jejunostomy due to abdominal pain - required a period of TPN whilst analgesia regimen optimised	Less social stigma Improved energy levels	Yes	In situ	Yes	3 years
6	Nausea improved, occasional vomiting Mild abdominal pain	Initially had issues with leakage however resolved with jejunostomy exchange	Cyclical EN feeds Approximately 20% oral intake Weight stable	Great quality of life Currently working High energy levels Improved social life	No	In situ	Yes	2 years
7	Improved nausea and abdominal pain	Hypergranulation tissue	Continuous EN feeds initially however now able to maintain nutrition *via* oral intake	Maintain oral nutrition Social and work life much improved Less leakage	Yes	Removed - able to maintain adequate oral nutrition	Yes	1.5 years

				compared to previous feeding tubes				
8	Improved nausea and abdominal pain	Nil	Cyclical EN initially however symptoms improved to the point where could tolerate oral intake	Regained independence Socially discrete Improved function at work Able to maintain nutrition orally	No	Removed - able to maintain adequate oral nutrition	Yes	2 years

EN: Enteral nutrition; TPN: Total parenteral nutrition; NJT: Nasojejunal tube.

Table 3 Quality of life domains - improvements and ongoing challenges

Specific domains	
Improvements	
Social functioning	Reduce visibility of the feeding tube
	Increased confidence in public settings
	Better ability to participate in social activities
Work/study	Improved attendance
	Better concentration
	Reduced interruptions for tube management
Physical wellbeing	Better symptom control
	Improved energy levels
	Weight stabilization
Independence	Easier self-care
	Greater mobility
	Reduced hospital visits
Ongoing challenges	
Physical activity	Exercise limitations due to tube position concerns about tube displacement during activity
	Travel considerations
Social life	Concerns about body image
	Managing feeding schedule around social activities
Work/study	Managing feeding schedules at work/class
	Finding private spaces for tube care
	Explaining medical needs to employers/educational institution
Sleep	Finding comfortable sleeping positions
	Managing overnight feeds
	Concern about tube displacement during sleep

CONCLUSION

In conclusion, this qualitative retrospective cohort study offers valuable patient-centered insights into Roux-en-Y jejunostomy as a potential option for long-term enteral support in gastroparesis. While the procedure had challenges and was not a panacea, the quality-of-life improvements described by most patients, along with the ability of some to transition to oral nutrition, justify further research to optimize patient selection, post-operative care, nutritional outcomes and complication management with this approach. Future research priorities should include: (1) Long-term outcome studies examining tube longevity, complication rates, and quality of life impacts beyond the initial post-operative period; (2) Comparative effectiveness studies *vs* other feeding tube approaches; (3) Investigation of patient factors (age, disease

severity, comorbidities) that may predict procedural success; and (4) Evaluation of optimal patient selection criteria and pre/post-operative management protocols. Additionally, studies incorporating validated instruments to measure quality of life, stigma, and nutritional outcomes would provide more robust evidence to guide clinical decision-making. Roux-en-Y jejunostomy may be a viable therapeutic option for carefully selected patients with gastroparesis requiring long-term tube feeding.

FOOTNOTES

Author contributions: Salehi O and Gao WL conducted patient interviews, performed data collection and analysis, prepared the figures and tables, and wrote the manuscript; Salehi O conducted thematic analysis of interview transcripts and coordinated study logistics; Gao WL assisted with data interpretation and manuscript revisions; Hebbard G conceptualized and designed the study, provided clinical oversight and critically revised the manuscript for important intellectual content; Kenfield C developed the surgical approach, provided technical expertise, contributed to study design, and critically reviewed the manuscript; and all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Royal Melbourne Hospital, approval No. QA2022100.

Informed consent statement: All involved participants gave their verbal informed consent prior to study inclusion. All participants provided informed consent prior to completing the questionnaire. Identifying details were removed during analysis to protect patient privacy. Participants were assigned a unique ID number for reference.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Predictive value of serum calcium ion level in patients with colorectal cancer: A retrospective cohort study

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Abstract

BACKGROUND

Serum calcium ion (Ca^{2+}) is an economical and readily available indicator as a routine screening test for hospitalized patients. There are no studies related to serum Ca^{2+} level and digestive tract malignancy.

AIM

To evaluate the effectiveness of serum Ca^{2+} level in predicting the prognosis of patients with colorectal cancer (CRC).

METHODS

We retrospectively collected the data of 280 patients diagnosed with CRC who underwent radical surgery at the Affiliated Cancer Hospital of Xinjiang Medical University. By analyzing the clinicopathological features, differences between serum Ca^{2+} concentrations on the first day after surgery were determined. We used the receiver operating characteristic curve to assess the predictive ability of serum Ca^{2+} for survival. Survival analyses were performed using the Kaplan-Meier method, and multivariate Cox proportional risk regression was used to determine association between calibration serum Ca^{2+} levels and CRC survival outcomes.

RESULTS

By receiver operating characteristic curve analysis, the ideal threshold value for Ca^{2+} the first postoperative day and delta serum calcium (δCa^{2+}) value were 1.975 and 0.245, respectively. Overall survival (OS) and progression-free survival (PFS)

were better in both the high Ca^{2+} group and high δCa^{2+} group on the first postoperative day. The variables identified through univariate analysis were incorporated into multivariate analysis and showed that tumor differentiation ($P = 0.047$), T stage ($P = 0.019$), N stage ($P < 0.001$), nerve vascular invasion ($P = 0.037$), carcinoembryonic antigen ($P = 0.039$), baseline serum Ca^{2+} level ($P = 0.011$), and serum Ca^{2+} level on the first day ($P = 0.006$) were independent predictors of prognosis for patients undergoing feasible radical CRC surgery. Using the findings from the multifactorial analysis, we developed a nomogram and the calibration showed a good predictive ability.

CONCLUSION

Low serum Ca^{2+} level on the first postoperative day is an independent risk factor for OS and PFS in CRC.

Key Words: Serum calcium ion; Colorectal cancer; Prognosis; Nomogram; Overall survival

Core Tip: Serum calcium ion (Ca^{2+}) is a readily available and cost-effective marker used in routine screenings but has not been studied in relation to digestive tract malignancies until now. This study examined the association of serum Ca^{2+} concentrations with clinical indicators in patients with colorectal cancer (CRC) undergoing radical surgery. The results show that reduced serum Ca^{2+} concentrations on the first day after surgery are associated with poorer overall survival and progression-free survival in patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC) is one of the malignant tumors with high morbidity and mortality worldwide. According to statistics, CRC ranks third among malignant tumors worldwide, accounting for approximately 10% of all cancer cases[1]. In recent years, with the change of lifestyle and the acceleration of population aging, the incidence and mortality rates of CRC in China have gradually increased. Compared with other regions of the world, the incidence and mortality rates of CRC in China are at an intermediate level[2]. Treatment options for CRC depend on the stage of the disease and the overall health of the patient. Surgical resection is the primary treatment for early-stage CRC, while chemotherapy and radiation may be used in the advanced stages to shrink the tumor and control symptoms[3]. Survival rates for patients with CRC are improving with the development of new treatment options and earlier detection methods. However, the disease remains a significant health burden. If one or a group of clinical test indicators can be found to assist in predicting prognosis, it may prolong the survival time of patients with CRC.

Calcium (Ca^{2+}), as one of the most important electrolytes in the body, is a very versatile second messenger that is involved in the regulation of various pathophysiological processes[4]. This includes regulators of cellular activities such as signaling[5], hormone secretion[6], glycogen metabolism[7], and cellular mitosis[8]. Extracellular Ca^{2+} is not only a source of intracellular Ca^{2+} but also plays an important role in the maintenance and stabilization of the cell wall and the formation of blood clots[9]. Most of the current studies on Ca^{2+} and tumors have focused on the effects of intracellular Ca^{2+} on tumorigenesis and development. Less research has been conducted on the relationship between serum Ca^{2+} levels and tumors. However, it has been shown that serum Ca^{2+} levels are associated with clinicopathologic processes such as nutritional status[10], inflammatory response[11], and lipid metabolism[12]. In the colonic environment, dietary Ca^{2+} binds to bile acids, thereby reducing the carcinogenic and pro-tumor effects of bile acids on colonic tissue, while intracellular Ca^{2+}, which is mainly derived from circulating Ca^{2+}, plays a greater role in inhibiting the proliferation of normal and neoplastic colorectal epithelial cells, promoting differentiation and apoptosis.

Studies have shown that storage-operated Ca^{2+} channel-regulated Ca^{2+} entry is involved in inflammation and CRC progression[13,14]. Recent evidence suggests that intracellular Ca^{2+} remodeling may contribute to cancer hallmarks[15]. Ca^{2+} intake also has beneficial effects on reducing the incidence of CRC and improving survival in several observational studies[16,17]. The findings of a prospective study conducted in Sweden indicated that there was a positive correlation between the concentration of circulating albumin-corrected serum total Ca^{2+} and the risk of CRC[18]. On the contrary, two large European prospective cohort studies indicated that higher levels of serum Ca^{2+} were associated with reduced risk of CRC development[19].

Serum Ca^{2+} is an economical and readily available indicator as a routine screening test for hospitalized patients. There are no studies related to serum Ca^{2+} level and digestive tract malignancy. Based on the above findings, we hypothesize that serum Ca^{2+} level may play a role in predicting the prognosis of patients with CRC.

MATERIALS AND METHODS

Study populations

The present study retrospectively and consecutively collected data on patients with CRC attending Xinjiang Medical University Cancer Hospital (Xinjiang, China) between 2016 and 2018. The inclusion criteria included: (1) Pathologic diagnosis of definite CRC; (2) Patients with radical resection; (3) Complete clinical case data; and (4) Complete follow-up data. The exclusion criteria included: (1) Those with previous or concurrent other primary cancer foci; (2) Those who underwent neoadjuvant radiotherapy or traditional Chinese medicine; (3) Those who have had two or more surgeries; (4) Death caused by non-CRC factors; and (5) Serious diseases that affect blood Ca^{2+} levels (*e.g.*, hypercalcemia, hypocalcemia). Based on the sample size, a total of 280 patients' medical records were collected.

Data collection

All clinicopathological data were obtained from the Department of Case Management of the Affiliated Cancer Hospital of Xinjiang Medical University. With reference to the relevant high-quality literature research indexes at home and abroad in the past 5 years and combined with the actual situation of our hospital, 15 research indexes were collected[20,21]. Specifically, they included age, sex, ethnicity, body mass index (BMI), tumor growth site, tumor stage, degree of differentiation, microsatellite stability, neural vascular invasion, carcinoembryonic antigen (CEA), baseline carbohydrate antigen 19-9 (CA19-9), baseline serum Ca^{2+} levels, serum Ca^{2+} level on the first postoperative day, and delta serum calcium (δCa^{2+}). Baseline indexes were defined as the results of the first laboratory test on admission. The δCa^{2+} value was defined as the absolute value of the baseline serum Ca^{2+} value minus the serum Ca^{2+} value on the first postoperative day.

The primary study endpoint was overall survival (OS), defined as the time from first admission or diagnosis to death or final follow-up. The secondary study endpoint was progression-free survival (PFS), defined as the time from first admission or diagnosis to first progression (including progression events such as local recurrence and distant metastasis). The Ethics Committee of the Affiliated Cancer Hospital of Xinjiang Medical University approved the ethical review after reviewing that the study complied with ethical principles (No. G-2015021). Written informed consent was obtained from all participants. The cutoff for follow-up was observation of the outcome event or 60 months of follow-up. Median follow-up time was 30 months.

Statistical analyses

Depending on the distribution of the data, continuous variables are described as the mean ± SD or median (Q1 to Q3). Categorical variables are expressed as absolute numbers or percentages. For normally distributed data, the independent samples *t*-test was used for differences between two groups, otherwise the Mann-Whitney *U* test was used. For comparisons between groups Fisher's exact test and Pearson's χ^2 test were used. The accuracy of baseline serum Ca^{2+} levels, δCa^{2+} values, and serum Ca^{2+} levels on the first postoperative day for prognostic prediction was evaluated by using receiver operating characteristic curve (ROC). The δCa^{2+} value and the serum Ca^{2+} level on the first postoperative day were selected as prognostic indicators based on the area under the ROC curve (AUC). The cut-off value was determined from the Youden index derived from the ROC, and the cut-off value for the δCa^{2+} value was 0.245 and the cut-off value for the serum Ca^{2+} level on the first postoperative day was 1.975. Based on the cut-off value results, the data were categorized into δCa^{2+} high group and low group, and postoperative day 1 serum Ca^{2+} high group and low group, and Kaplan-Meier curves were plotted separately, and the differences were assessed using log-rank test. Independent risk factors for OS and PFS were determined by univariate and multivariate Cox regression analyses. Nomograms of 1-year, 3-year, and 5-year survival of patients with CRC were plotted using the R software package "rms." Next, internal validation of the nomogram was performed using the bootstrap method. Calibration curves were used to assess the agreement between predicted and observed survival. Decision curve analysis was used to assess the clinical utility of the nomogram. All statistical tests were two-sided and differences were considered statistically significant at $P < 0.05$. All statistical data were analyzed with SPSS 26.0 (IBM SPSS Statistics, Armonk, NY, United States), GraphPad Prism 10.0 (GraphPad Software, Boston, MA, United States), and R4.2.0. The description of baseline information, Spearman's rank correlation analysis, and Cox regression analysis were performed using SPSS, and ROC and Kaplan-Meier curves were generated using GraphPad Prism. Noetherian and calibration plots were drawn in R using the rms package. Models were compared using the "survcomp" package. All statistical tests were two-sided and differences were considered statistically significant at $P < 0.05$.

RESULTS

Patients' characteristics

In this study, clinical data of 280 patients were collected by combining inclusion and exclusion criteria. They were categorized into 179 patients in the high-level group and 101 patients in the low-level group based on the critical value of serum Ca^{2+} on the first postoperative day. In comparing the baseline data, there were significant differences between the two groups in terms of age ($P = 0.012$), degree of tumor differentiation ($P = 0.018$), CEA ($P = 0.002$), Ca^{2+}-baseline (mmol/L) ($P = 0.005$), and δCa^{2+} value ($P < 0.001$) (Table 1). There were no significant differences between race and sex groups.

Ca^{2+}-related indicators predict prognostic value

To assess the predictive value of serum Ca^{2+} levels in patients with CRC, we performed ROC analysis of baseline serum

Table 1 Baseline data of 280 patients with colorectal cancer, *n* (%)

Characteristics		Ca^{2+}-first postoperative day		*P* value
		High group (> 1.975 mmol/L)	Low group (< 1.975 mmol/L)	
n		179	101	
Ethnic group				0.821
	Han ethnic group	149 (83.2)	83 (82.2)	
	Others	30 (16.8)	18 (17.8)	
Sex				0.693
	Female	77 (43.0)	41 (40.6)	
	Male	102 (57.0)	60 (69.4)	
Age (years)				0.012[a]
	< 65	121 (67.6)	53 (52.5)	
	≥ 65	58 (32.4)	48 (47.5)	
BMI				0.383
	< 23.5	65 (36.3)	42 (41.6)	
	≥ 23.5	114 (63.7)	59 (58.4)	
Tumor location				0.709
	Right half of colon	37 (22.6)	19 (15.1)	
	Left half of colon	142 (77.4)	82 (84.9)	
Degree of differentiation				0.018[a]
	High differentiation	24 (13.4)	3 (3.0)	
	Moderately differentiated	127 (70.9)	80 (79.2)	
	Poorly differentiated	28 (15.6)	18 (17.8)	
T stage				0.313
	T1-2	39 (21.8)	21 (20.8)	
	T3	106 (59.2)	53 (52.5)	
	T4	34 (19.0)	27 (26.7)	
N stage				0.907
	0	102 (54.7)	55 (52.3)	
	N1	48 (45.3)	28 (47.7)	
	N2	29 (16.2)	18 (17.8)	
Neurovascular invasion				0.463
	No	133 (74.3)	79 (78.2)	
	Yes	46 (25.7)	22 (21.8)	
MSI				0.698
	MSS	164 (91.6)	94 (93.1)	
	MSI-H	15 (8.4)	7 (6.9)	
CEA (ug/L)				0.002[a]
	< 5	129 (72.1)	54 (53.5)	
	≥ 5	50 (27.9)	47 (46.5)	
CA19-9 (U/mL)				0.304
	< 39	158 (85.8)	90 (90.7)	

	≥ 39	21 (14.2)	11 (9.3)	
Hb (g/L)				0.753
	< 120	50 (27.9)	30 (29.7)	
	≥ 120	129 (72.1)	71 (70.3)	
PLT (10^9/L)				0.641
	< 330	143 (79.9)	83 (82.2)	
	≥ 330	36 (20.1)	18 (17.8)	
Alb (g/L)				0.175
	< 40	65 (36.3)	45 (44.6)	
	≥ 40	114 (63.7)	56 (55.4)	
Ca^{2+}-baseline (mmol/L)				0.005[a]
	< 2.11	24 (7.5)	11 (9.3)	
	≥ 2.11	155 (92.5)	90 (90.7)	
δCa^{2+}				< 0.001[a]
	< 0.245	145 (81.0)	28 (27.7)	
	≥ 0.245	34 (19.0)	73 (72.3)	

[a]$P < 0.05$.

δCa^{2+}: Delta serum calcium value; Alb: Albumin; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9; Ca^{2+}-baseline: Baseline serum calcium ion levels; Ca^{2+}-first postoperative day: Serum calcium ion level on the first day of postoperative period; CEA: Carcinoembryonic antigen; Hb: Hemoglobin; MSI: Microsatellite; PLT: Platelet.

Ca^{2+} levels and δCa^{2+} values. The baseline serum Ca^{2+} level AUC was 0.502, the AUC on the first postoperative day was 0.655 with a critical value of 1.975, and the δCa^{2+} value AUC was 0.625 with a critical value of 0.245 (Figure 1). Restricted cubic spline revealed a nonlinear relationship between Ca^{2+}-first postoperative day and hazard ratio (HR) in patients with CRC. The results showed that HR gradually decreased with the increase of Ca^{2+} (Figure 2). This suggests that Ca^{2+}-first postoperative day is a patient-protective factor.

Correlation studies of serum Ca^{2+} levels on the first postoperative day with other studied variables

Spearman's rank correlation analysis was conducted on age, sex, ethnic group, BMI, CEA, CA19-9, hemoglobin, blood platelet, albumin and serum Ca^{2+} level (high and low group) on the first postoperative day to analyze the variables related to serum Ca^{2+} level on the first postoperative day. Age, ethnic group, CEA, and CA19-9 were inversely associated with serum Ca^{2+} levels on the first postoperative day. Age ($P < 0.001$) and CEA ($P = 0.002$) were significant with serum Ca^{2+} levels on the first postoperative day. BMI ($P = 0.042$) and albumin ($P = 0.005$) were positively correlated with serum Ca^{2+} levels on the first postoperative day, and the correlation was equally significant (Table 2).

Survival analyses

Kaplan-Meier analysis was conducted on survival differences between δCa^{2+} groups and high and low serum Ca^{2+} levels on the first postoperative day. We found that the OS time was shorter in the δCa^{2+} high group, with a statistically significant difference between the two groups (log-rank $P = 0.0079$, HR = 1.954) (Figure 3A). The higher serum Ca^{2+} level was longer in the group, with a statistically significant difference between the two groups (log-rank $P = 0.0007$, HR = 0.415) (Figure 3B). Similarly, in the PFS analysis, patients in the δCa^{2+}-high group had shorter PFS (log-rank $P = 0.0007$, HR = 2.385) (Figure 3C), and patients with higher serum Ca^{2+} level on the first day after surgery had a longer PFS (log-rank $P = 0.0003$, HR = 0.3867) (Figure 3D).

Univariate analysis and multivariate analyses

Univariate analysis using Cox regression analysis showed that tumor differentiation ($P < 0.001$), T stage ($P < 0.001$), N stage ($P < 0.001$), nerve vascular invasion ($P < 0.001$), CEA ($P < 0.001$), baseline serum Ca^{2+} ($P = 0.042$), serum Ca^{2+} on the first postoperative day ($P < 0.001$), and δCa^{2+} value ($P = 0.010$) were associated with the prognosis of patients undergoing feasible radical CRC surgery. The variables selected by univariate analysis were included in multivariate analysis, which showed that tumor differentiation ($P = 0.047$), T stage ($P = 0.019$), N stage ($P < 0.001$), nerve vascular invasion ($P = 0.037$), CEA ($P = 0.039$), baseline serum Ca^{2+} level ($P = 0.011$), and serum Ca^{2+} level on the first day ($P = 0.006$) were independent risk factors affecting the prognosis of patients undergoing feasible radical CRC surgery (Table 3).

Establish and evaluate the prediction model

Based on the results of multivariate analysis, we selected sex, N stage, and serum Ca^{2+} level on the first postoperative day

Table 2 Correlation between clinical data variables and serum calcium ion levels on the first postoperative day

Relevant factor	Spearman's correlation coefficient	*P* value
Age (years)	-0.253	< 0.001[a]
Sex	0.003	0.963
Ethnic group	-0.038	0.600
BMI	0.148	0.042[a]
CEA	-0.224	0.002[a]
CA19-9	-0.035	0.673
Hb	0.129	0.075
PLT	0.052	0.476
Alb	0.203	0.005[a]

[a]$P < 0.05$.

Alb: Albumin; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; Hb: Hemoglobin; PLT: Platelet.

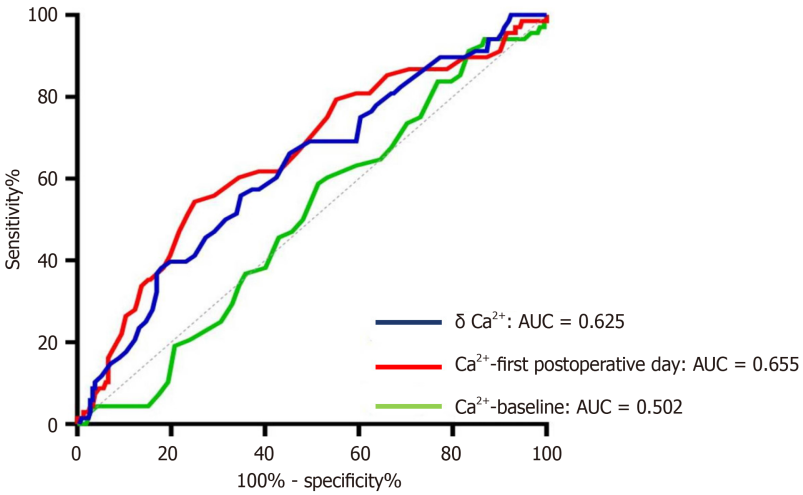

Figure 1 Receiver operating characteristic curve of serum calcium ion-related indicators to predict outcome. δCa^{2+}: Delta serum calcium; AUC: Area under the receiver operating characteristic curve; Ca^{2+}-baseline: Baseline serum calcium ion levels; Ca^{2+}-first postoperative day: Serum calcium ion level on the first day of postoperative period.

to establish a nomogram to predict the OS of patients undergoing feasible radical CRC surgery (Figure 4). The calibration curves of 1-, 3-, and 5-year OS illustrated good calibration between the predicted and actual survival probabilities in the whole cohort (Figure 5). Additionally, decision curve analysis further confirmed the significant clinical efficacy of this nomogram model in predicting survival probabilities at 1, 3, and 5 years (Figure 6).

DISCUSSION

In this study, through retrospective analysis of the clinical case data of 280 CRC patients in our hospital from 2016 to 2018, we found that the decrease in postoperative Ca^{2+} level and the large fluctuation of preoperative and postoperative Ca^{2+} level were independent risk factors for the prognosis of patients with feasible radical CRC surgery. Meanwhile, a correlation was found between the postoperative Ca^{2+} level and multiple clinical characteristics and blood indicators. The prognostic prediction model with sex, N stage, and serum Ca^{2+} level on the first postoperative day as variables had good predictive value.

Ca^{2+} is one of the essential nutrients in the human body. It exists in the form of Ca^{2+} in the blood, which is the most abundant cation in the human body[22]. In addition to its involvement in bone mineralization[23], it is also essential for maintaining the normal function of nerves[24], muscles[25], and the heart[26]. The main direction of previous Ca^{2+} research is in it as a signaling molecule mediating various physiological mechanisms and participating in various physiopathological activities[27]. Most studies on serum Ca^{2+} concentration and tumors have focused on multiple myeloma and parathyroid tumors[28]. Mainly because the above two tumors themselves can cause changes in the serum

Table 3 Univariate and multivariate analyses of clinicopathological data in patients with colorectal cancer

Characteristics	Univariate analysis, HR (95%CI)	*P* value	Multivariate analysis, HR (95%CI)	*P* value
Ethnic group		0.610	-	-
Han ethnic group				
Others	0.840 (0.429-1.643)			
Sex		0.021[a]		0.031[a]
Female				
Male	1.848 (1.097-3.115)		1.796 (1.056-3.054)	
Age (years)		0.622	-	-
< 65				
≥ 65	1.134 (0.688-1.867)			
BMI (kg/m^2)		0.448	-	-
< 23.5				
≥ 23.5	0.830 (0.513-1.343)			
Tumor location		0.387	-	-
Right half of colon				
Left half of colon	1.330 (0.697-2.535)			
Degree of differentiation		< 0.001[a]		0.047[a]
High differentiation				
Moderately differentiated	3.250 (0.788-13.399)	0.103	2.056 (0.483-8.753)	0.330
Poorly differentiated	8.192 (1.920-34.960)	0.004[a]	3.717 (0.845-16.348)	0.082
T stage		< 0.001[a]		0.019[a]
T1-2				
T3	3.272 (1.290-8.303)	0.013[a]	1.447 (0.518-4.037)	0.481
T4	5.820 (2.220-15.261)	< 0.001[a]	2.874 (1.034-7.985)	0.043[a]
N stage		< 0.001[a]		< 0.001[a]
0				
N1	2.063 (1.150-3.702)	0.015[a]	1.321 (0.696-2.509)	0.394
N2	4.575 (2.564-8.164)	< 0.001[a]	3.407 (1.763-6.586)	< 0.001[a]
Neurovascular invasion		< 0.001[a]		0.037[a]
No				
Yes	2.576 (1.588-4.178)		1.820 (1.036-3.196)	
MSI		0.234		
MSS				
MSI-H	0.495 (0.156-1.575)			
CEA (ng/mL)		< 0.001[a]		0.039[a]
< 5				
≥ 5	2.398 (1.489-3.863)		1.709 (1.027-2.845)	
CA19-9 (U/mL)		0.148		
< 39				
≥ 39	1.611 (0.844-3.073)			
Hb (g/L)		0.389		

< 120				
≥ 120	0.800 (0.481-1.330)			
PLT (10^9/L)		0.284		
< 330				
≥ 330	1.358 (0.776-2.379)			
Alb (g/L)		0.636		
< 40				
≥ 40	0.890 (0.549-1.443)			
Ca^{2+}-baseline		0.042[a]		0.011[a]
< 2.11				
≥ 2.11	3.326 (1.045-10.584)		4.762 (1.426-15.905)	
Ca^{2+}-first postoperative day		< 0.001[a]		0.006[a]
High				
Low	2.234 (1.387-3.597)		2.315 (1.276-4.199)	
δCa^{2+}		0.010[a]		0.506
Low				
High	1.876 (1.166-3.020)		0.820 (0.458-1.471)	

[a]$P < 0.05$.

δCa^{2+}: Delta serum calcium; Alb: Albumin; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9; Ca^{2+}-first postoperative day: Serum calcium ion level on the first day of postoperative period; CEA: Carcinoembryonic antigen; CI: Confidence interval; Hb: Hemoglobin; HR: Hazard ratio; MSI: Microsatellite; PLT: Platelet.

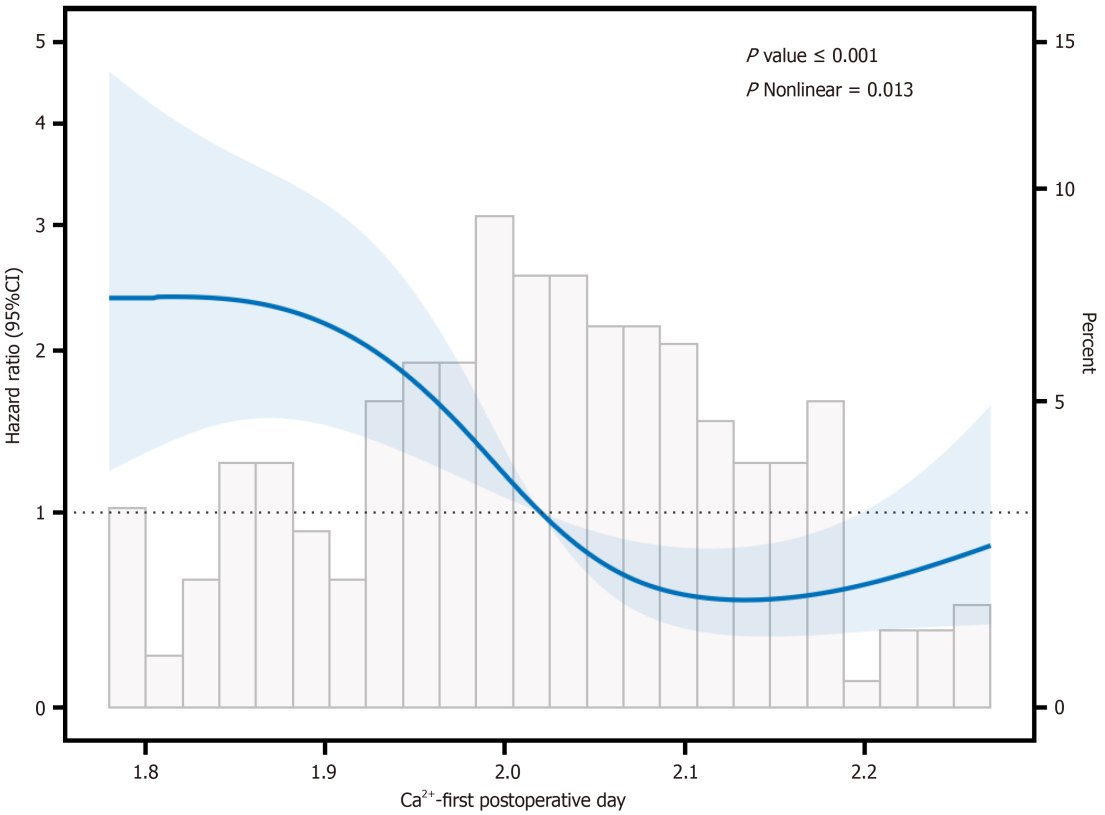

Figure 2 Restricted cubic spline curves for serum calcium ion level on the first day of the postoperative period in colorectal cancer. Ca^{2+}-first postoperative day: Serum calcium ion level on the first day of postoperative period; CI: Confidence interval.

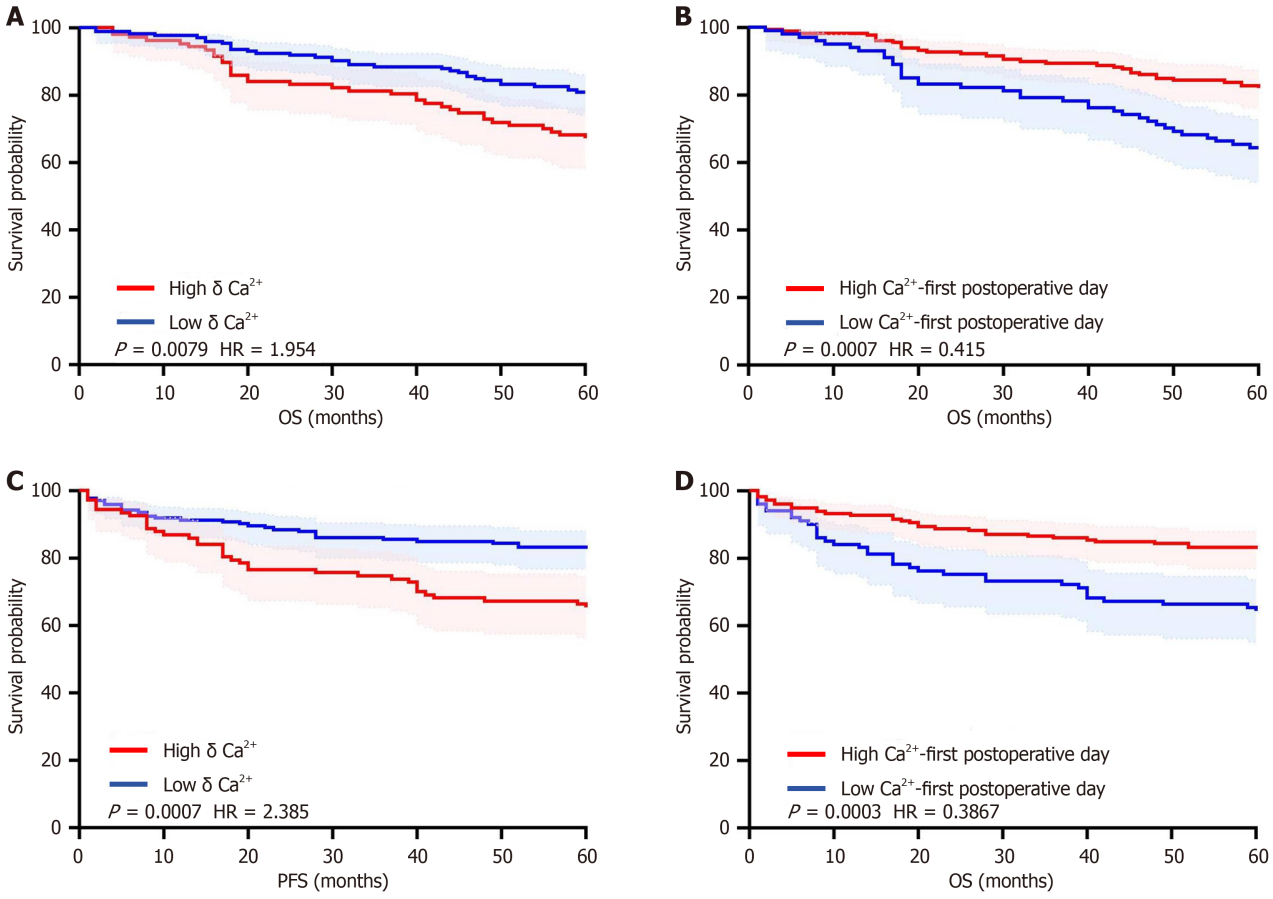

Figure 3 Overall survival and progression-free survival stratified by Δ calcium value and serum calcium ion level on the first day of postoperative period. A: Overall survival (OS) stratified by delta serum calcium (δCa^{2+}) value (P = 0.0079, hazard ratio [HR] = 1.954); B: OS stratified by serum Ca^{2+} ion level on the first day of postoperative period (Ca^{2+}-first postoperative day) (P = 0.0007, HR = 0.415); C: Progression-free survival (PFS) stratified by δCa^{2+} value (P = 0.0007, HR = 2.385); D: PFS stratified by Ca^{2+}-first postoperative day (P = 0.0003, HR = 0.3867).

Ca^{2+} level, and the serum Ca^{2+} level has been widely recognized as a tumor marker of the above tumors[29]. However, the relationship between serum Ca^{2+} and other malignancies has not been widely verified. This study started from clinical data and found that serum Ca^{2+} levels were associated with the prognosis of patients with CRC. In particular, the postoperative serum Ca^{2+} level is an independent risk factor affecting the prognosis of patients with CRC with feasible radical surgery.

In recent years, it has been reported that aspirin can inhibit the proliferation of CRC cells, mainly relying on the manipulation of Ca^{2+} influx in the Ca^{2+} pool by its main metabolite, salicylate[30]. Aspirin, as an adjuvant drug, can enhance the effects of neoadjuvant chemoradiotherapy and improve the prognosis of patients with rectal cancer. For patients with CRC treated with preoperative neoadjuvant therapy, the combination of aspirin may be considered a better choice[31]. However, as aforementioned, the main direction of these studies is that Ca^{2+} plays a role in tumor proliferation as a signaling molecule in the cell. It has also been reported that increasing Ca^{2+} intake may be associated with prevention of colon adenoma and improving CRC prognosis. This literature also points to the same important role in the development and development of colorectal tumors[32]. This study was only used as a clinical observational study and did not monitor and analyze serum Ca^{2+} levels.

With the improvement of people's living standards and the increase of obesity, BMI as a risk factor for the development of CRC has been confirmed[33]. Murphy *et al*[34] found limited evidence of heterogeneity between BMI and CRC risk, suggesting that obesity affects almost all the major pathways involved in colorectal carcinogenesis. However, BMI is not a risk factor for CRC in patients with Lynch syndrome[34]. Our study found a correlation between postoperative Ca^{2+} level and patients' BMI, which may also be one of the reasons for the correlation between Ca^{2+} level and prognosis. Meanwhile, the involvement of Ca^{2+} in lipid metabolism has been clearly confirmed[12]. On the one hand, Ca^{2+} can activate certain enzymes and promote the decomposition and oxidation of fatty acids, helping to regulate the fat levels in the body. On the other hand, Ca^{2+} also participate in the balance of intestinal microbial flora, and play an important role in maintaining intestinal health. Studies have shown that lipid metabolism disorders can lead to imbalance of intestinal flora and damage of intestinal mucosa, which leads trigger inflammatory response and oxidative stress. These responses can damage intestinal mucosal cells, causing abnormal hyperplasia and mutation, eventually leading to the development of CRC. Moreover, disturbed lipid metabolism can also affect cell signaling and gene expression, further contributing to the development of CRC. Therefore, it is necessary to determine whether the change of Ca^{2+} level reflects lipid metabolism to some extent and further affects the prognosis of CRC.

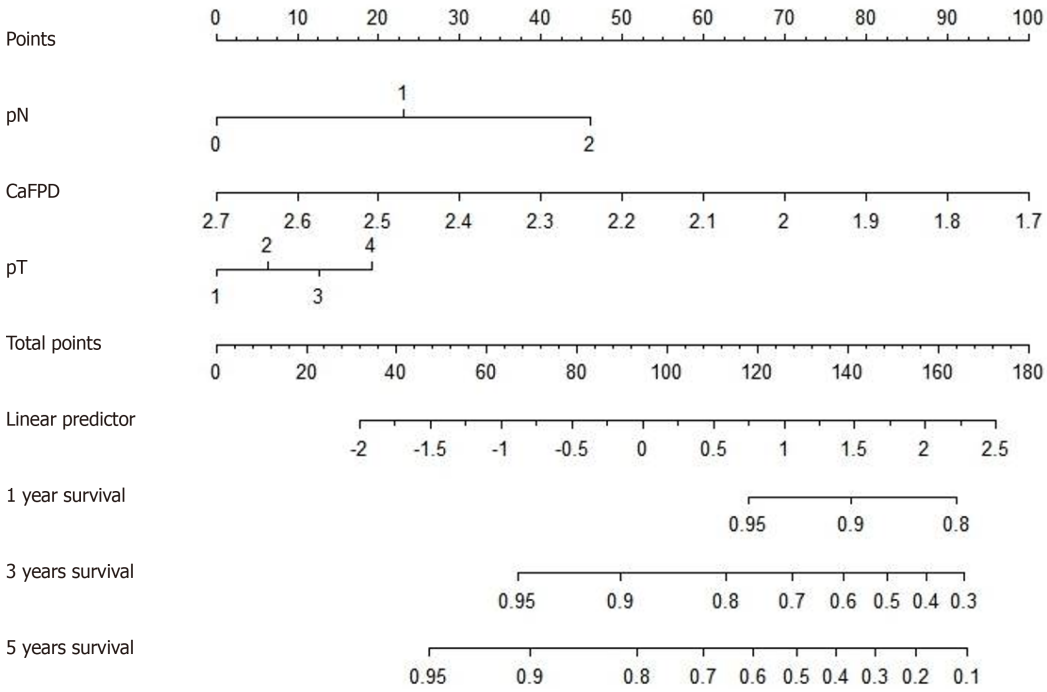

Figure 4 Nomograph of the model composed of T stage, N stage, and serum calcium level on the first postoperative day. CaFPD: Calcium level on the first postoperative day.

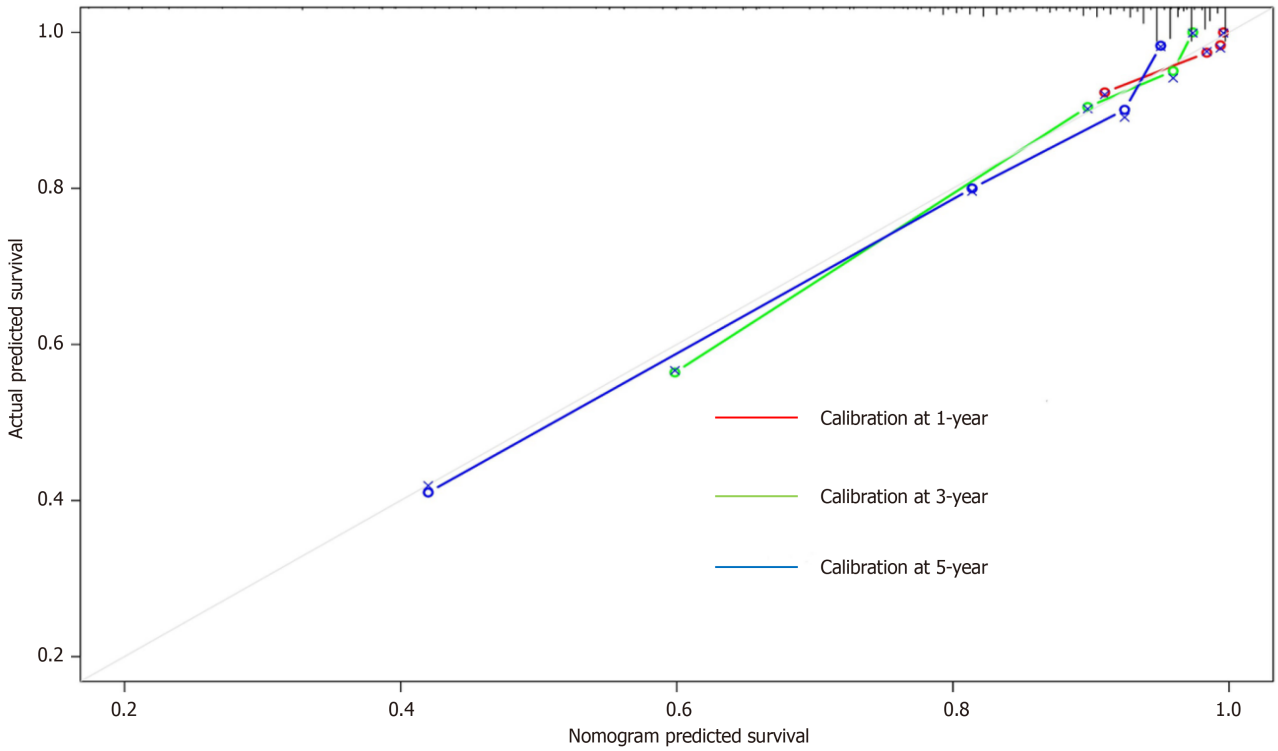

Figure 5 Calibration curves to predict 1-year, 3-year, and 5-year overall survival.

With the growth of age, the body's ability to absorb Ca^{2+} gradually decreases, resulting in decreased Ca^{2+} levels in the body[35]. The alteration of free Ca^{2+} concentration in the cytoplasm, in combination with other signal-transduction cascades, regulates a variety of cellular processes through a universal signaling mechanism. The involvement of several protein kinases is responsible for intracellular Ca^{2+} signaling and homeostasis, leading to numerous physiological and pathological consequences, such as cell cycle, proliferation, apoptosis, gene transcription, cell migration arrangement and regulation. It is therefore not surprising that certain Ca^{2+}-mediated signaling pathways are implicated in tumorigenesis and progression[36]. The dysregulation of Ca^{2+} is implicated in driving a diverse array of cancer pathways, which may manifest as tissue-specific, context-specific, or universal among different types of cancers. Previously overlooked in the

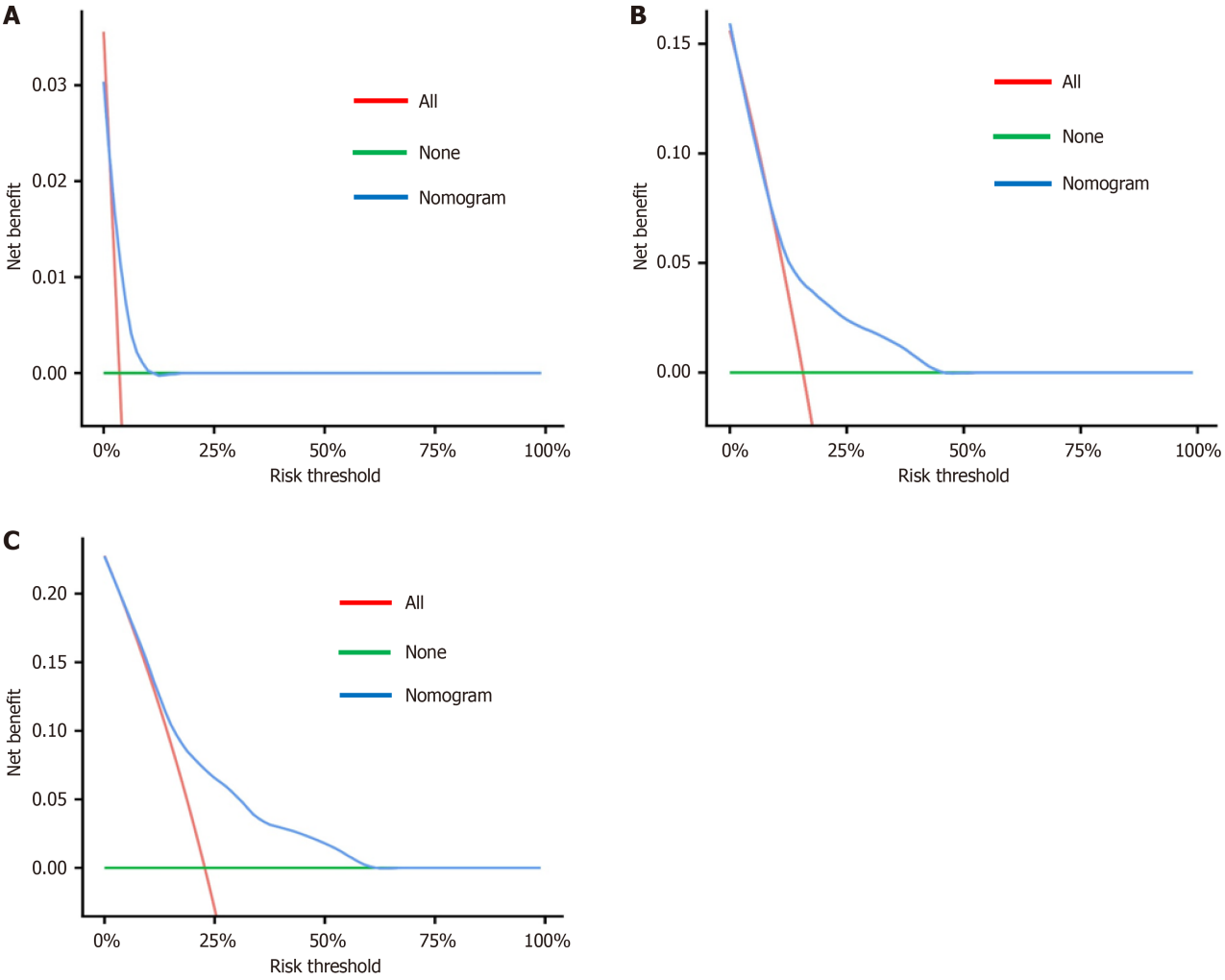

Figure 6 Decision curve analyses with clinical net benefits of the nomogram at 1 year, 3 years, and 5 years. A: Decision curve analyses with clinical net benefits of the nomogram at 1 year; B: Decision curve analyses with clinical net benefits of the nomogram at 3 years; C: Decision curve analyses with clinical net benefits of the nomogram at 5 years.

realm of cancer research, the regulation of Ca^{2+} presents a promising avenue for developing future context-specific treatments for various forms of cancer[37]. There are specific differences in pathological characteristics and clinical characteristics between middle-aged and middle-aged patients in patients with CRC. In this study, we conducted statistical analyses of the age of both groups by using the postoperative Ca^{2+} level as the basis for grouping. The results showed a statistically significant difference in age between the two groups. However, due to the small sample size of this study, further stratification analysis was not conducted to clarify the specific correlation with the level of Ca^{2+} in elderly patients and the role of the prognostic impact. In the future, we need to clarify the relationship between the postoperative Ca^{2+} level and the age through more in-depth research to provide a scientific basis for improving the surgical effect of elderly patients.

A key step in cancer progression is metastasis, which is largely driven by an invasive process known as epithelial-mesenchymal transition (EMT). When epithelial cells adopt a mesenchymal cell phenotype, they exhibit changes in anterior-posterior polarity conformation, which enhances migration and invasiveness to increase cancer metastasis. EMT is induced by a variety of growth factors[38]. These include epidermal growth factor, fibroblast growth factor and transforming growth factor beta. Although these growth factors utilize disparate mechanisms to promote EMT, it is notable that the majority of these factors rely on Ca^{2+} signaling to fulfil their biological roles[39]. Ca^{2+} signaling plays a pivotal role in EMT by driving the expression of mesenchymal marker genes and promoting extracellular matrix degradation[37].

Albumin is one of the important nutrients in the blood, which can reflect the nutritional status of the individual. Changes in albumin levels in postoperative patients, which are usually considered important indicators for assessing rehabilitation status and nutritional status. Nutritional status is clearly related to the prognosis of various malignant tumors, especially colorectal malignant tumors as one of the digestive tract tumors, and nutritional status is particularly important in affecting its prognosis. Clinical data from multiple studies show that malnutrition is a risk factor for poor prognosis[40]. In this study, a significant correlation between postoperative Ca^{2+} levels and albumin levels by spearman correlation analysis. This finding reveals us the potential role of Ca^{2+} in the assessment of nutritional status. This correlation may be one of the reasons why postoperative Ca^{2+} affects the prognosis and should be supported by further

clinical data.

The fact that Ca^{2+} participate in inflammatory responses through multiple pathways is a widely validated fact[41]. The decrease in Ca^{2+} levels was obvious in patients with heavy inflammatory response. Some studies show that serum Ca^{2+} serves as an important monitoring index of the intensive care department, and its high and low changes are related to the prognosis of severe patients[42]. Studies have shown that the inflammatory response is an independent risk factor for prognosis in patients with CRC, while the inflammatory response affects the response to immunotherapy in some types of patients with CRC. This study found that reduced Ca^{2+} levels in postoperative patients was a prognostic risk factor. It also seems not difficult to understand the results of this study in terms of the level of inflammatory response. However, how serum Ca^{2+} acts on the development of CRC are not clear. Meanwhile, most of the patients in this study received adjuvant chemotherapy after surgery, and whether the serum Ca^{2+} level affected the therapeutic effect of chemotherapy in this part of patients deserves a more in-depth study.

There this study had some limitations. This study was a single-center retrospective cohort study with a small sample size, which does not allow for more stratified analyses to reveal the deeper significance and value of serum Ca^{2+} levels in the development of CRC. Second, studies on Ca^{2+} metabolism and gastrointestinal tumor development must consider not only serum Ca^{2+} levels but also dietary intake and factors regulating Ca^{2+} homeostasis, including serum vitamin D and parathyroid hormone levels. The present study was conducted mainly in a single hospital, with a relatively small sample size and covering only patient populations in a specific region. To improve the breadth of the study and the external validity of the conclusions, a multicenter, large-sample study design should be considered in the future, covering patients from different regions and populations. This will help us better understand the association between chronic diseases and blood Ca^{2+} levels in different regions and pathologic contexts. In the current study, we included hypertension, diabetes mellitus, cardiovascular and cerebrovascular diseases, and chronic obstructive pulmonary disease as overall covariates in the model, but in reality, these chronic diseases may have different subtypes and clinical phenotypes in the clinical setting. For example, patients with hypertension may be grouped into subtypes based on disease duration, control, comorbidities, and so on; patients with diabetes may be further categorized based on glycated hemoglobin levels, insulin use, and so on. Therefore, future studies should consider a more detailed stratified analysis to reveal the different effects of chronic disease subtypes on blood Ca^{2+} levels. Many patients with chronic diseases are often accompanied by multiple medications, and these medications (*e.g.*, antihypertensive agents, hypoglycemic agents, antiplatelet agents) may have direct or indirect effects on blood Ca^{2+} levels, bone metabolism, and cardiovascular function. Future studies could incorporate patients' medication history to explore the potential relationship between pharmacologic interventions and blood Ca^{2+} levels. This would provide a more precise basis for clinical management, especially in patient populations with multiple co-morbidities. Lifestyle (*e.g.*, diet, exercise, smoking, alcohol consumption) is an important factor influencing chronic disease and health status; however, this paper failed to systematically consider the potential impact of lifestyle on the study findings. Future studies could incorporate lifestyle factors into analytic models to explore how they affect blood Ca^{2+}levels and disease management in patients with chronic diseases. In addition, intervention studies (*e.g.*, improved diet, increased exercise) would be useful in assessing the long-term effects of lifestyle changes on chronic diseases and related biomarkers (*e.g.*, blood Ca^{2+}).

This study relied primarily on an internal validation set to evaluate the model; however, internal validation alone does not allow for a comprehensive assessment of the applicability and accuracy of the model in different patient populations. To improve the external validation of the model, future studies will introduce independent validation datasets, especially from different regions, different clinical settings or patient populations with different characteristics. This will help to assess the model's ability to generalize and ensure its stability and accuracy across different populations. In addition to assessing the accuracy of the model through external validation sets, attention should also be paid to the performance of the model in actual clinical applications. For example, clinical trials or prospective studies can be conducted to track the impact of the model on patient management, treatment decisions, and prognosis prediction in the real world. Long-term follow-up data will help assess the continued stability and clinical validity of the model.

However, we can still draw inspiration from this study, especially in clinical work, whether appropriate Ca^{2+} supplementation would improve the prognosis of CRC patients. For cancers of the digestive tract such as CRC, nutrition and inflammation have a great impact on the prognosis of patients. Serum Ca^{2+} reflect the nutritional and inflammatory status of patients, and they are also very easy to obtain in the clinic. We can intervene in advance by preoperative and postoperative Ca^{2+} levels to improve the prognosis of patients. This may provide some guidance in our future clinical patient management. The Ca^{2+} levels in this study were all concentrated around 7-10 days after the patients were first admitted to the hospital, so we were unable to analyze the long-term changes in Ca^{2+} levels and whether long-term changes in Ca^{2+} levels would affect the prognosis of patients with CRC. However, this is one of the questions we would like to address, *i.e.* whether prognosis can be predicted earlier after a patient's diagnosis, as is the case with postoperative Ca^{2+} supplementation, thus helping the clinic to implement more aggressive treatments for patients and improve prognosis.

CONCLUSION

In conclusion, our findings suggest that Ca^{2+} on the first postoperative day is an independent prognostic biomarker affecting OS and DFS in patients with CRC. Ca^{2+} on the first postoperative day may be a practical biomarker for prognostic prediction in laryngeal and pharyngeal tumors.

FOOTNOTES

Author contributions: Shu Y was responsible for the study design, data acquisition, and preliminary analysis, and also took the lead in drafting the initial manuscript; Li KJ made significant contributions to the data analysis and interpretation, and played a key role in revising and improving the manuscript; Shu Y and Li KJ designed the article format, collected the data, and wrote the manuscript; Sulayman S, Zhang ZY, Ababaike S, Wang K, Zeng XY, and Chen Y were responsible for the statistical analyses; Zhao ZL designed the main study and critically revised the manuscript; All authors read and approved the final manuscript. Both authors made equal contributions to the study and as co-first authors of this manuscript.

Institutional review board statement: The Ethics Committee of Affiliated Cancer Hospital of Xinjiang Medical University approved the ethical review after reviewing that the study complied with ethical principles (No. G-2015021).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at zlzhao71@163.com. Participants gave informed consent for data sharing.

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ORIGINAL ARTICLE

Retrospective Study

Impact of a visual mobile terminal-based continuity of care model on caregiver competence of children with enterostomies

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Abstract

BACKGROUND

Children with critical acute abdominal conditions often undergo intestinal stoma surgery.

AIM

To explore the impact of a visual mobile terminal-based extended care model on caregiver competence for children with enterostomies.

METHODS

One hundred twenty children with enterostomies and their caregivers in a children's hospital in Beijing were divided into a control group and a study group. The control group (60 cases) received traditional telephone follow-up for continuity of care, while the study group (60 cases) used a visualization mobile terminal-based care model. The incidence of stoma-related complications, caregiver burden scale, and competence scores of children with stoma were compared between the two groups.

RESULTS

The primary caregiver burden score in the study group (37.22 ± 3.17) was significantly lower than that in the control group (80.00 ± 4.47), and the difference was statistically significant ($P < 0.05$). Additionally, the caregiving ability score of the study group (172.08 ± 3.49) was significantly higher than that of the control group (117.55 ± 4.28; $P < 0.05$). The total incidence of complications in the study group (11.7%, 7/60) was significantly lower compared to the control group (33.3%, 20/60; $\chi^2 = 8.086$, $P = 0.004$).

CONCLUSION
The visual mobile terminal-based care model reduces caregiver burden, improves home care ability, lowers the incidence of complications and readmission rates, and supports successful second-stage reduction surgery for children with enterostomies.

Key Words: Mobile terminal; Enterostomy; Continuity of care; Caregiver burden; Visual mobile terminal; Caregiver competence; Stoma care; Caregiver competence

Core Tip: This study examines a novel visual mobile terminal-based continuity of care model for children with enterostomies. Comparing traditional telephone follow-up (control group) to the new model (study group), significant improvements were observed. The study group exhibited lower caregiver burden scores (37.22 *vs* 80.00), higher caregiving ability scores (172.08 *vs* 117.55), and reduced stoma-related complications (11.7% *vs* 33.3%). This innovative approach enhances caregiver competence, decreases complications, and reduces readmission rates, laying a robust foundation for successful second-stage surgery in children with enterostomies.

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INTRODUCTION

Children with severe abdominal infection, strangulated intestinal obstruction, intestinal necrosis, congenital megacolon crisis, and other critical acute abdominal conditions often undergo intestinal stoma surgery. This surgery creates a temporary opening, and stomas are closed within three to six months after the initial surgery[1,2]. Providing high-quality care during this period is crucial due to the special characteristics of the pediatric population, poor compliance, and the general lack of expertise of caregivers and the special characteristics of the colostomy.

Therefore, providing professional continuity of care to such families and caregivers is essential to reducing complications and improving the quality of life for these children[3,4]. The rapid development of the Internet and the increasing use of social networking tools in healthcare services have increased the demand for health services for children and families[5]. The stoma conditions of children can be assessed through an information-based health education model using mobile terminals, forming a hospital-family visualization and interaction model of continuity of care.

This study examines the impact of a visual, mobile terminal-based continuity of care model on the competence of caregivers of children with enterostomies, comparing it to a traditional continuity of care model.

MATERIALS AND METHODS

Study design and participants

Children with enterostomies and their caregivers admitted to the Department of Children's Surgery of a tertiary-level children's hospital in Beijing participated in this study. The study was conducted from May 2020 to May 2021. The participants were divided into two groups: A control group (hospitalized from May 2020 to November 2020) and a study group (hospitalized from December 2020 to May 2021). To be included in the study, children had to meet the following criteria: (1) Underwent temporary enterostomy in our hospital but have not yet undergone reversal surgery; (2) Younger than 6 months old; (3) Able to use smartphones with a regular companion or a companion who can use smartphones with the assistance of other family members; (4) Stable network signal during the period of residence; and (5) Their caregivers were aware of, and voluntarily participated in, the study. Children were excluded from the study if they met any of the following criteria: (1) Had severe underlying conditions or malignant tumor; (2) Required full-time hospitalization for care after stoma surgery; (3) Had caregivers who were paid service workers; or (4) Had data with invalid entries. This study was approved by the Hospital Ethics Committee (Ethics No. 2021-21).

Determination of sample size

The readmission rate due to complications was used as an estimation index. The difference between the baseline and general information of the two groups was not statistically significant ($P > 0.05$) and is comparable, as shown in Table 1.

Table 1 Comparison of general information of children and caregivers in the two groups, *n* (%)

Groups	Number of examples	Sex of child		Age at admission (days)	Stoma site		Stoma type		Caregiver qualifications			Age of caregiver (years)
		Male	Daughter		Ileum (anatomy)	Second section of large intestine	Single lumen	Double lumen	Three-year college	Undergraduate (adjective)	Bachelor's degree	
Research group	60	39 (65.9)	21 (35.0)	28.0 ± 2.6	38 (63.8)	22 (36.3)	20 (32.5)	40 (67.5)	33 (55.0)	23 (38.8)	4 (6.3)	32.7 ± 4.4
Control subjects	60	45 (74.7)	15 (25.3)	28.2 ± 2.4	42 (66.7)	18 (33.3)	18 (31.6)	42 (68.4)	32 (53.2)	23 (38.0)	5 (8.9)	32.8 ± 4.5
t or χ^2 value		1.429		-0.369	1.280		0.154		0.126			-0.082
P value		0.232		0.713	0.258		0.695		0.939			0.935

Methods of intervention

Control group: Routine nursing measures were implemented during the hospitalization of the child with an enterostomy. One day after the replacement of the stoma bag, the child and the caregiver were introduced to the characteristics of the stoma products, the process of replacing the stoma bag, and the timing, skills, and key points. Before discharge, caregivers were instructed to operate independently once, with the nurse responsible for their care, who corrected irregular operations promptly. Monthly telephone follow-ups were conducted after discharge. The telephone follow-up program includes specific components such as psychological care, feeding support, stoma care skills, guidance on complications, daily care instructions, and reminders for follow-up visits. Primary caregivers are provided with a fixed phone number for the department, allowing them to call with any questions they may have. The on-duty nurse for that day is responsible for addressing the caregivers' inquiries and providing the necessary assistance and any issues were addressed at the hospital outpatient clinic.

Study group: In addition to the routine telephone and outpatient follow-up after discharge, a visualized mobile terminal was applied to carry out informative nursing intervention as follows: (1) Formation of a mobile terminal intervention group (a total of 10 members were formed, including the head nurse of the department as the team leader, two deputy chief physicians of pediatric surgery, two international wound stoma therapists, one network engineer, and four nurses who had been engaged in the specialty of pediatrics for more than 5 years; (2) Training of group members (the head nurse and deputy chief physician trained the nurses on stoma care techniques, common complications and care of stoma, characteristics of various dressings, cutting and fixation, stoma photo techniques, stoma-related health education points, stoma care assessment and records, stoma informed consent notification); Training was conducted through nursing workshops, academic salons, experience sharing, specialized training, joint room visits, and teleconsultation; and (3) Specific division of labor (team members worked together to develop the program). The head nurse was responsible for coordination and management, the consultant solved complex clinical problems, the network engineer maintained the network and published the public numbers, and the international stoma therapist searched for literature, compiled questionnaires, and formulated the nodes and main contents of the stoma-related knowledge push. The team implemented the specific intervention and assisted the international stoma therapist in integrating the contents, pictures, and video shooting. The specific implementation interventions are shown in Table 2 and Supplementary material.

Evaluation indicators

Application of the caregiver competency measurement scale for children with intestinal stomas: The research team developed the Caregiver Competency Measurement Scale for Children with Intestinal Stomas. We invited 11 experts in related fields to conduct two rounds of consultation and conducted a pre-survey of 20 caregivers. The scale includes six dimensions: Stoma knowledge comprehension (five entries), stoma care operation skills (five entries), infant daily life care (six entries), nutritional development monitoring of children with enterostomies (seven entries), recognition and management of enterostomies and complications (seven entries), and caregiver executive ability (seven entries), totaling 38 entries. The scale was based on a 5-point Likert scale, ranging from 1 (not able to do at all) to 5 (able to do at all), with the total score being the sum of the scores of each entry. A higher score indicates a better ability of the caregiver to take care of the child. The Cronbach's coefficient of the scale was 0.855.

Caregiver's burden inventory: The nurses collected the Caregiver's burden inventory (CBI)[6] through mobile terminal and telephone follow-ups in the study and control groups one month after the children were discharged from the hospital. The scale contains five dimensions: Time-dependent burden, developmentally limited burden, physiological burden, social burden, and emotional burden, and 24 entries; each entry was rated on a 5-point scale of 0-4 points based on the severity of the burden, with the total score ranging from 0-96 points. A higher total score indicates a heavier burden. The scale has good reliability and validity, with a Cronbach's α coefficient of 0.875.

Caregiver burden scale: The caregiver burden scale was collected from the study and control groups after one month of hospitalization.

Table 2 Main contents of terminal visualization modules and functions

Terminal visualization modules and functions	Fortunate timing	Thrust	Formality
Poll	The day of admission	The system uploads the results to the server for the team to view, count and analyze the basic information of the child and the disease information	Forms, questionnaires
	Day of discharge	Caregiver satisfaction questionnaires, which allow caregivers to evaluate the mobile terminal model of care and provide comments and suggestions on the work of the medical staff in the department	Poll
Nodalized push of stoma knowledge	The day of admission	Introduction to the department, basic knowledge about stoma, dietary instruction, use of mobile terminals and precautions	Graphic, video
	1 day before discharge	How to take pictures of children with stoma-related problems and precautions, the process of discharge-related procedures, preparation of pre-discharge supplies, main points to observe during the home stay, outpatient clinic visit time and review time	Graphic
	1 week after discharge	Preventive measures such as sending precautions and care measures for stoma-related complications that may occur in children, and educating caregivers about mental health and caregiving tips	Graphic, video
	3 weeks after discharge	Caregiving capacity questionnaire, dietary guidance	Forms, questionnaires
	2 months after discharge	Basic data collection form and re-admission process of the child, reminding parents to prepare supplies on time for admission procedures, in preparation for the second stage of reduction surgery	Forms, questionnaires, graphics
Image/video visualization capabilities	during home stay	Group nurses retrieve photos of children's problems from the background every day and distribute them to doctors or stoma therapists according to the problem attributes, so that healthcare professionals can visually and effectively solve children's existing problems, give real-time nursing guidance to caregivers, and provide explanations on key points of nursing care and how to use the products	Graphic, video
Text/voice message function	During home stay	Out-of-hours caregivers can leave a message for consultation, and healthcare professionals can follow up with the child and caregiver online and provide professional psychological care to the caregiver	Text, voice

Incidence of complications: The incidence of unplanned readmission and stoma-related complications (stoma prolapse, stoma retraction, parastomal hernia, and irritant dermatitis) was compared between the two groups of children from discharge to the time of reduction surgery.

Statistical analysis

Data were analyzed using SPSS 21.0. Count data were described by frequency and rate, and comparisons between groups were made using the χ^2 test or Fisher's exact probability method. Measurement data were described by mean ± SD. Comparisons between groups were made using the *t*-test. A *P*-value of less than 0.05 ($P < 0.05$) was considered statistically significant.

RESULTS

Comparison of primary caregiver caregiving capacity scores between the two groups

The competence scores of the primary caregivers in the study group were significantly higher than those of the control group at one month after the intervention, and the difference was statistically significant ($P < 0.05$; Table 3).

Comparison of primary caregiver care burden scores between the two groups

The primary caregiver burden score of the study group was significantly lower than that of the control group at one month after the intervention, and the difference was statistically significant ($P < 0.05$; Table 4).

Comparison of the incidence of stoma complications between the two groups of children before and after the study

The overall incidence of complications in the study group (11.7%, 7/60) was lower than that in the control group (33.3%, 20/60), and the difference was statistically significant ($\chi^2 = 8.086$, $P = 0.004$; Table 5).

Table 3 Comparison of post-intervention caregiving competence scores between the two groups of caregivers, points

Groups	Number of examples	Ostomy knowledge comprehension	Ostomy care skills	Daily life care for infants	Nutritional development monitoring in children with enterostomies	Recognizing and responding to colostomy and peripheral complications	Caregiver implementation	Totals
Research group	60	22.85 ± 1.83	27.10 ± 1.34	26.00 ± 1.69	31.97 ± 1.18	32.10 ± 1.26	32.07 ± 1.22	172.08 ± 3.49
Control subjects	60	11.92 ± 1.34	18.58 ± 1.38	17.97 ± 1.35	22.90 ± 2.00	23.03 ± 1.67	23.15 ± 1.95	117.55 ± 4.28
t value		39.282	34.165	28.774	30.282	33.498	30.065	76.404
P value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Table 4 Comparison of post-intervention care burden scores of primary caregivers in the two groups

Groups	Number of examples	The time-dependent burden	Burden of development constraints	Physiological burden	Social burden	Emotional burden	CBI total score
Research group	60	9.83 ± 1.68	6.12 ± 1.28	3.17 ± 1.04	8.73 ± 1.56	9.37 ± 1.43	37.22 ± 3.17
Control subjects	60	16.97 ± 1.59	17.18 ± 1.60	12.33 ± 1.96	12.58 ± 2.22	20.93 ± 1.77	80.00 ± 4.47
t value		-23.865	-41.882	-31.935	-10.992	-39.363	-60.433
P value		< 0.001	< 0.001	< 0.001	0.002	< 0.001	< 0.001

CBI: Caregiver's burden inventory.

Table 5 Complications in the two groups of children, *n* (%)

Groups	Number of examples	Stoma dermatitis	Stoma prolapse	Stoma	Stoma retraction	Parastomal hernia
Research group	60	2 (3.8)	1 (1.3)	1 (1.3)	1 (1.3)	2 (3.8)
Control subjects	60	7 (11.4)	2 (3.8)	4 (6.3)	2 (3.8)	5 (7.6)
χ^2 value		3.003	[1]	[1]	[1]	1.365
P value		0.083	0.559	0.171	0.559	0.243

[1]Fisher's exact probability method.

DISCUSSION

Continuity of care enables comprehensive and systematic nursing care for children with enterostomies from admission to discharge and throughout their transition from hospital to home[7]. This approach allows families to effectively manage the home care period, addressing challenges as they arise underscoring the holistic nature of care[8]. Without a consistent care plan and standardized guidance from professional caregivers, children with stomas who are discharged from the hospital and cared for at home are prone to various problems, such as diarrhea, dehydration, and malnutrition due to inadequate diet, which can be life-threatening in severe cases[9]. Additionally, improper handling of the stoma bag, such as not securing it properly, falling off, or the leaking out of feces due to the inability of the caregiver to change the stoma bag, can lead to complications such as inflammation of the skin around the stoma[10]. Therefore, the difficulty of postoperative care and the burden of family care for children with enterostomies are significantly higher than that for adults. The competence of caregivers in pediatric stoma care greatly affects the outcome of second-stage re-institutionalization surgery and the overall health of children with stomas[10,11].

With the rise of the "Internet +"[12], more industries are integrating with the Internet[13] and the nursing industry is no exception. To provide more convenient and effective continuity of care services, nursing experts have created a variety of communication platforms on the Internet to meet the needs of patients[14,15]. Wound stoma care has gradually embraced this trend, with nursing scholars creating stoma web platforms to meet the care and communication needs of patients with stomas and their families. Dabas *et al*[16] developed a 9-minute video teaching program (VTP) for pediatric entero-

stomies, which improved the theoretical knowledge and practical skills of the caregivers after two weeks of use. The mobile terminal-based informational health education model uses information technology to assess the stoma condition of the child. Based on these assessments, professional disease knowledge and stoma care guidance are provided to the caregivers through various visual forms on the WeChat public platform, such as text, pictures, video, and voice[5,17]. This model enhances the knowledge of the child and the caregiver about the disease, strengthens their confidence in the treatment, and reduces the complication rates.

The study indicates that, following the intervention, the burden of care scores for primary caregivers in the study group was significantly lower than those in the control group ($P < 0.05$). Primary caregivers of children with stomas face numerous challenges, including those related to the disease, stoma care, daily life stress, social functionality loss, as well as difficulties arising from the child's limited language expression, sensitive skin, and weakened immunity. These challenges often contribute to negative psychological emotions. The application of a mobile terminal-based continuity of care model facilitated regular dissemination of health knowledge to primary caregivers. This approach enhanced caregivers' understanding of the prevention, treatment, and rehabilitation of stoma-related complications. Additionally, timely responses to caregivers' questions promoted communication and strengthened the effectiveness of health education, thereby deepening emotional connections with medical personnel. Knowledge was delivered in a timely sequence, effectively alleviating the caregivers' physiological, temporal, emotional, and social burdens. Post-intervention, the caregiving ability scores of primary caregivers in the study group were significantly higher than those of the control group ($P < 0.05$). The caregivers' skills are crucial for improving the quality of care and safeguarding the rights of patients. Through educational content presented in multimedia formats, such as images, text, and videos, caregivers were able to better understand and master the key steps of stoma care. Notably, VTP and the integration of text with images greatly facilitated caregivers in learning and mimicking proper caregiving techniques, thereby improving the accuracy of stoma care procedures. The continuity of care model delivered through mobile terminals allowed caregivers to address many caregiving issues at home, reducing the risk of infections and other complications associated with frequent hospital visits. The implementation of this visual mobile terminal continuity of care model resulted in a lower incidence of complications in children with stomas; the overall complication rate in the study group was significantly lower than that in the control group ($P = 0.004$). By utilizing this visual mobile terminal continuity of care model, primary caregivers gained greater knowledge and skills for self-management, thus effectively performing daily care and preventing complications. This timely and convenient access to information significantly enhanced the awareness of health knowledge and facilitated the prompt identification and management of potential complications, ultimately leading to a reduction in the incidence of stoma-related complications.

This study shows that this continuity of care model can improve the ability of the caregivers to care for their children. The visual mobile terminal extended care model uses nodes to push stoma care knowledge through pictures, words, and videos, helping caregivers better master stoma care skills. It also proactively sends information about potential stoma-related problems at different time nodes and provides solutions, enabling caregivers to learn and prepare in advance, to reduce the sense of helplessness of the caregiver when the child has a problem[18]. This continuity of care model can meet the needs of child caregivers who use fragmented time to learn about stoma care during their stay at home, improve stoma care skills, and enhance the ability of the caregiver to care for the child.

The present study showed that the caregiver burden score was significantly lower in the study group after the intervention. The incidence of stoma-related complications was also significantly lower in the study group compared to the control group. Ostomy-related complications can reduce the quality of life of the children, affect late fistula surgery, and can be life-threatening in severe cases. Through online voice and video communication, caregivers can communicate directly with the healthcare personnel at home, making problem-solving more precise and effective. The combination of graphics and text aids mutual understanding and corrects misconceptions. Through the mobile terminal, child caregivers can proactively acquire and apply stoma-related knowledge in daily life and care processes, which is more targeted and personalized than the traditional issuance of publicity brochures[19]. Caregivers can improve their nursing skills through online learning, thereby reducing the incidence of stoma-related complications, thus improving the outcome of the child [20]. The study was conducted with a small sample, which imposed inherent limitations. Future studies should expand the sample size and refine the continuity of care model using a visualization mobile terminal.

CONCLUSION

In summary, visualized mobile terminal extended care can update the knowledge of relevant diseases for the caregivers and provide accurate one-to-one accurate services to address their problems promptly. It can also effectively reduce the CBI score, improve the caregiver competence of children with enterostomies, and reduce the incidence of complications during home care.

FOOTNOTES

Author contributions: Yu Y wrote the paper; Wang XQ and Liu G analyzed the data; Xia Q, Li L, and Chen LN planned the study; Yu Y and Zhang LJ executed the study and collected most of the data. All authors contributed to drafting the article and revised the manuscript for important intellectual content. All authors had access to the study data and reviewed and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Optimal timing of endoscopic biliary drainage for bile duct leaks: A multicenter, retrospective, clinical study

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Abstract

BACKGROUND

Bile duct leaks (BDLs) are serious postsurgical adverse events. Typically, conservative management with abdominal drainage is the initial treatment option. However, prolonged abdominal drainage without improvement can lead to biliary stricture and delay the optimal timing of endoscopic retrograde cholangiopancreatography (ERCP).

AIM

To identify the optimal timing for ERCP and the period during which clinical observation with conservative management is acceptable, balancing ERCP success and the risk of biliary strictures.

METHODS

We conducted a multicenter retrospective study involving 448 patients with BDLs between November 2002 and November 2022. The patients were divided into four groups based on the timing of ERCP: 3 days, 7 days, 14 days, and 21 days. The primary outcome was clinical success, defined as the resolution of BDL and related symptoms within 6 months without additional percutaneous drainage, surgery, or death. The secondary outcome was incidence of biliary strictures. Univariate and multivariate logistic regression analyses were performed to identify factors associated with ERCP success and biliary stricture occurrence.

RESULTS

In a cohort of 448 consecutive patients diagnosed with BDLs, 354 were excluded, leaving 94 patients who underwent ERCP. Clinical success was achieved in 84% of cases (79/94), with a median ERCP timing of 20 days (9.5-35.3 days). Biliary strictures were identified in 29 (30.9%) patients. Performing ERCP within 3 weeks, compared to after 3 weeks, was associated with higher success rates [92.0% (46/50) *vs* 75.0% (33/44), $P = 0.032$] and a lower incidence of biliary stricture incidence [18.0% (9/50) *vs* 45.5% (20/44), $P = 0.005$]. Subsequent multivariate analysis confirmed the association with higher success rates (odds ratio = 4.168, $P = 0.045$) and lower biliary stricture rates (odds ratio = 0.256, $P = 0.007$).

CONCLUSION

Performing ERCP for BDLs within 3 weeks may be associated with a higher success rate and a lower biliary stricture rate. If patients with BDLs do not respond to conservative treatment, ERCP is suggested to be performed within 3 weeks.

Key Words: Endoscopic retrograde cholangiopancreatography; Bile duct leaks; Endoscopic nasobiliary drainage; Endoscopic biliary stent drainage; Optimal timing; Biliary stricture

Core Tip: In this multicenter study, 94 patients with bile duct leaks who underwent endoscopic retrograde cholangiopancreatography (ERCP) were retrospectively analyzed. We found that performing ERCP within 3 weeks was associated with higher success rates and a lower incidence of biliary stricture than later interventions. Multivariate analysis confirmed that early ERCP was a key factor for improved outcomes. If patients with bile duct leaks do not respond to conservative treatment, ERCP is suggested to be performed within 3 weeks.

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INTRODUCTION

Bile duct leaks (BDLs) are common adverse events (AEs) associated with hepatobiliary surgery, including cholecystectomy, partial hepatectomy, and liver transplantation[1,2]. BDLs can result in potentially life-threatening conditions, including electrolyte imbalance, peritonitis, abdominal abscesses, or sepsis[3]. In clinical practice, a drainage tube is usually retained after hepatobiliary surgery or percutaneous drainage is performed if no drain is placed during surgery. Most BDLs can be conservatively managed with abdominal drainage. Therefore, observation and conservative treatment with abdominal drains are advisable[4]. During the observation period, improvements in symptoms, such as relief of abdominal pain, reduction in abdominal drainage fluid, and normalization of laboratory values, should be closely

monitored. If no symptom improvement occurs during the clinical observation period, endoscopic retrograde cholangiopancreatography (ERCP) is recommended. ERCP is an effective treatment for BDLs, with endoscopic biliary stent drainage and nasobiliary drainage as the primary techniques[5-7]. The rationale is to reduce the pressure gradient, promote preferential bile flow from the bile duct to the duodenum, and facilitate healing of BDLs[8].

Several studies have investigated the timing of ERCP on the outcome of BDLs and concluded that ERCP can be performed electively rather than urgently, with conservative management and observation recommended[9-11]. However, these studies did not specify an observation period, which could delay treatment and burden the patients. Prolonged BDLs may lead to infections and complications, making ERCP alone insufficient and requiring additional procedures. In addition, prolonged inflammation at the BDL site results in fibrosis and adhesive strictures[12]. Therefore, determining the optimal timing for ERCP is crucial to ensure successful outcomes without increasing the risk of biliary strictures. We conducted a multicenter retrospective study to examine the effect of ERCP timing on the success rate and occurrence of bile duct strictures in patients with BDLs. This study aimed to identify the optimal observation period for conservative management to ensure a high success rate with minimal risk of biliary stricture.

MATERIALS AND METHODS

Patients and data collection

We established a comprehensive database of six centers. All participating centers received training on the study objectives, case report form completion, and standardized data collection procedures. Medical data including basic demographic characteristics, laboratory test results, etiology of BDLs, characteristics of different methods, and procedural characteristics were collected and reviewed retrospectively.

The inclusion criteria were as follows: (1) Adults (> 18 years old); and (2) Either increasing or persistent bilious output from abdominal drainage, new fluid collection consistent with biloma on imaging studies, or extravasation of contrast outside the biliary tree on radiography. The exclusion criteria were as follows: (1) Inability to tolerate ERCP due to poor general condition; (2) Successful treatment with abdominal drainage and surgery; (3) Diagnostic ERCP; (4) Combined with advanced pancreatobiliary tumors; (5) Inability to reach the duodenal papilla *via* duodenoscope; and (6) Pregnancy. A total of 448 patients with BDLs who were treated between November 2002 and November 2022 were included. All patients provided informed consent before undergoing ERCP, and the study protocol was approved by the Ethics Committee of the Chinese PLA General Hospital, approval No. S2023-067-01. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Procedures

The procedures were performed by experts with > 10 years of experience in ERCP. Patients were placed in the prone position and received sedation or general intravenous anesthesia with close monitoring of their vital signs during the procedure. A duodenoscope (TJF-240/260; Olympus, Tokyo, Japan) was inserted into the descending part of the duodenum and carefully positioned at the papilla. Selective cannulation of the bile duct was performed using a papillotome or catheter directed toward the 11-12 o'clock position. After successful cannulation, cholangiography was performed to confirm the characteristics of the BDL and identify any associated stones or strictures. Under guidewire guidance, a biliary stent or nasobiliary drain was placed, with the aim of crossing over the leak site. Specific details of the procedure, including the need for endoscopic sphincterotomy and choice of biliary stent or nasobiliary drain in terms of length and diameter, were at the discretion of the endoscopist. If associated stones were present, stone retrieval was performed using a retrieval basket or balloon prior to drainage.

After the procedure, patients fasted and received symptomatic supportive treatment, including acid suppression, infection prevention, and fluid replacement. Vital signs and abdominal symptoms were closely monitored to observe for any postoperative complications. Follow-up examinations were scheduled 1 months, 3 months, and 6 months after the procedure. The nasobiliary drain was removed after cholangiography, indicating complete healing of the BDL. For patients with a biliary stent, stent exchange was performed every 3 months after the procedure until cholangiography confirmed leak closure.

Definitions and outcomes

The primary outcome was clinical success, whereas the secondary outcome was the incidence of biliary strictures. This study aimed to determine the optimal timing of ERCP for BDLs, and the period during which clinical observation with conservative management is acceptable, balancing ERCP success and the risk of biliary strictures. The optimal timing of ERCP was defined as the time point with a relatively high success rate and a low occurrence rate of biliary strictures. Clinical success was defined as the resolution of BDL and related clinical symptoms within 6 months without additional percutaneous drainage, surgery, or death[9,13]. The timing of ERCP was defined as the number of days from the hepatobiliary surgery or trauma to the initial ERCP. AEs were defined in accordance with the guidelines of the American Society of Gastrointestinal Endoscopy[14] and included pancreatitis, cholangitis, bleeding, perforation, and cardiopulmonary complications. The Charlson comorbidity index (CCI) was used to quantitatively analyze patient comorbidities[15]. Biliary stricture was defined according to the American College of Gastroenterology Clinical Guideline[16]. The location of the BDL was classified as the cystic duct, common bile duct, hilar bile duct, or intrahepatic bile duct.

Statistical analysis

Continuous data were reported as mean ± SD or median with interquartile range, as appropriate. Categorical data were presented as frequencies and proportions. The association between potential risk factors and ERCP success was evaluated using univariate analysis, namely Student's *t*-test and Wilcoxon rank-sum test for continuous data, and the χ^2 test and Fisher's exact test for categorical data. Potential factors with a *P* value lower than 0.1 in the univariate analysis and baseline variables considered clinically relevant were included in the multivariate logistic regression analysis. Odds ratios (OR) with 95% confidence intervals (CI) were calculated, and a two-sided *P*-value lower than 0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, United States).

RESULTS

Patients and therapeutic procedures

Total of 448 consecutive patients with clinically confirmed BDLs, 354 were excluded (Figure 1A). The final cohort of 94 patients (66 men, 28 women) had a mean age of 52.5 ± 12.9 years, a mean body mass index of 23.1 ± 3.4, and a median CCI score of 3 (interquartile range: 1-4). The etiologies of BDLs included cholecystectomy (69.1%), liver transplantation (13.8%), hepatectomy (8.5%), trauma (4.3%), and other causes (pancreatectomy and choledocholithotomy) (4.3%). The median timing of ERCP was 20 days (interquartile range: 9.5-35.3). The BDLs were located in the cystic duct (56.4%), common bile duct (21.3%), hilar bile duct (12.8%), and intrahepatic bile duct (9.6%). Seventy-six patients (80.9%) underwent abdominal drainage prior to ERCP. Plastic stents were used in most patients (55.3%), 10Fr plastic stents were used most frequently (35/53, 66.0%). Nasobiliary drainage tubes were used in 31 patients (33.0%), and metal stents were used in three patients (3.0%). The baseline characteristics, laboratory test results, and Strasberg classification of the 94 patients with BDLs are shown in Table 1.

Patient outcomes

Clinical success was achieved in 79 patients (84.0%), and the median duration from the primary ERCP to resolution was 89 days (interquartile range: 60-99 days). Among the 15 patients who did not achieve clinical success with ERCP, 14 required additional unplanned procedures, including surgery and percutaneous drainage, while one patient died of septic shock caused by BDLs. Biliary strictures were found in 29 patients (30.9%), and all strictures were located at the site of the leak. Twelve patients (12.8%) experienced AEs, including ten cases of pancreatitis, two cases of bleeding, and one case of cholangitis. All complications were classified as mild and successfully managed with medical treatment. The average number of ERCP procedures per patient was 1.3 ± 0.7 and most of the patients (84.8%, 67/79) needed only one ERCP to solve the BDLs. The median follow-up time was 29.6 months (interquartile range: 8.1-145.0 months), and none of the patients had recurrent BDLs during the follow-up.

Timing of ERCP and effect on success and biliary stricture

The median time from the initial injury to the initial ERCP was 20 days (interquartile range: 9.5-35.3). Considering previous studies, median timing, and clinical experience, we divided the patients into the following four groups according to the timing of ERCP: 3 days, 7 days, 14 days, and 21 days. After converting the timing of ERCP into a binary variable based on these time points, we summarized the success rate, biliary stricture rate, OR, and *P*-value at each time point (Table 2). Performing ERCP within 21 days resulted in higher success rates (OR = 3.833, 95%CI: 1.122-13.097, *P* = 0.032) and lower rates of biliary strictures (OR = 0.263, 95%CI: 0.103-0.670, *P* = 0.005). There were no statistically significant differences in basic demographics, laboratory test results, etiology of BDLs, treatment methods, or procedural characteristics between patients who underwent ERCP within 21 days and those who underwent ERCP after 21 days (Table 1).

Fifteen variables were analyzed to determine their influence on ERCP success. Univariate analysis revealed that body mass index (*P* = 0.049), CCI (*P* = 0.031), cystic duct disease (*P* = 0.002), and ERCP within 3 weeks (*P* = 0.032) were associated with clinical outcomes of ERCP (*P* < 0.1). Multivariable analysis was subsequently performed, and the following variables remained associated with ERCP success: ERCP within 3 weeks (OR = 4.168; 95%CI: 1.031-16.841, *P* = 0.045) and cystic duct leak (OR = 12.219; 95%CI: 2.317-64.433, *P* = 0.003) (Table 3). Similarly, 13 variables were analyzed for their potential association with biliary strictures. Univariate analysis indicated that CCI (*P* = 0.021), liver transplantation (*P* = 0.053), and ERCP within 3 weeks (*P* = 0.005) were potentially associated with biliary strictures (*P* < 0.1). Multivariate analysis showed that ERCP performed within 3 weeks was significantly associated with biliary strictures (OR = 0.256; 95%CI: 0.096-0.683, *P* = 0.007) (Table 4).

DISCUSSION

BDLs are serious AEs that usually occur after hepatobiliary surgery and trauma, leading to peritonitis, sepsis, or in severe cases, death[13,17]. ERCP is an important treatment option for BDLs, with relatively high success rates in some cases. In this retrospective study, ERCP demonstrated a clinical success rate of 84.0% for BDLs, which is consistent with the success rates reported in previous studies (71%-94.4%)[7,9,10,18-23]. Performing ERCP within 3 weeks, compared with after 3 weeks, was associated with higher success rates and lower biliary stricture incidence. Several studies have investigated

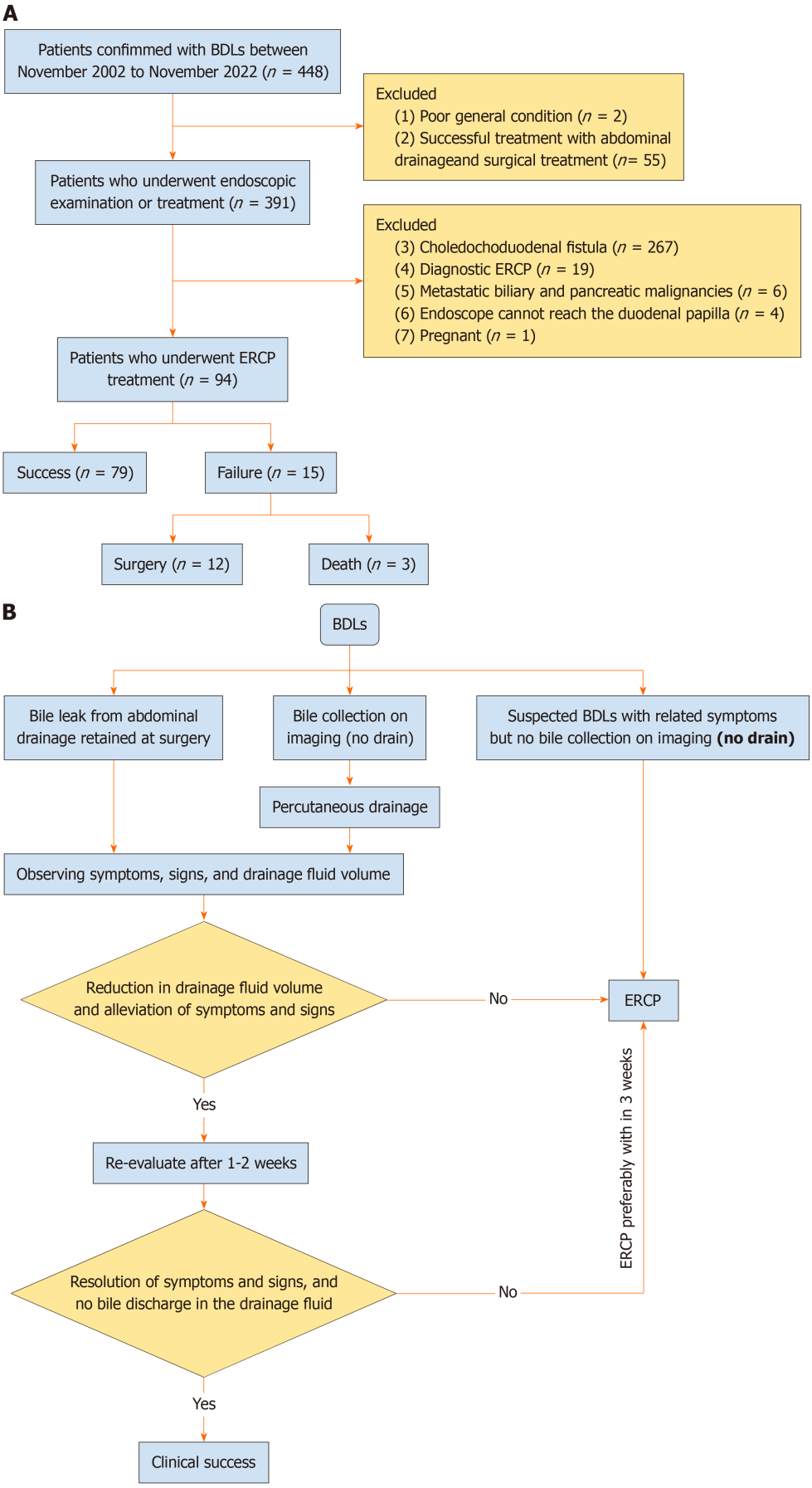

Figure 1 Flowchart of patients included in the study and flowchart of endoscopic retrograde cholangiopancreatography timing. A: Flowchart of patients included in the study; B: Flowchart on the timing of endoscopic retrograde cholangiopancreatography. BDLs: Bile duct leaks; ERCP: Endoscopic

retrograde cholangiopancreatography.

the effect of ERCP timing on the success rate of BDLs[9-11]. These studies categorized the timing of ERCP into < 1 day, 2-3 days, and > 3 days and found no statistically significant differences among the groups. These studies suggest that ERCP for BDLs can be performed electively rather than urgently. However, they did not specify an observation period, which may have burdened patients and delayed treatment.

Most cases of BDL can be treated with abdominal drainage tubes repaired during surgery, with a success rate ranging from 75% to 94%[24-29]. Viganò *et al*[25] reported a success rate of 76.5% in patients with BDLs within a median time of 15 days (range: 4-180 days). However, prolonged BDLs may result in intra-abdominal infections, sepsis, and other complications, making it difficult to manage BDLs with ERCP alone, requiring additional debridement or drainage procedures[4]. Persistent bile leakage may induce inflammation, leading to inflammatory strictures at the leak site[4,12]. In our study, 29 patients (30.9%) had no prior history of biliary stricture; however, biliary strictures at the site of the leak were discovered during ERCP, indicating that these biliary strictures are related to BDLs. In a retrospective study of 119 patients with bile duct injury and leakage, 21.8% had biliary strictures[30]. Lokesh *et al*[31]found that bile leaks lasting > 4 weeks increased the risk of biliary strictures, which is consistent with our study.

In contrast to previous studies, this study determined an acceptable observation period for conservative treatment, during which ERCP success rates remained high without increasing the risk of biliary strictures. The relationship between the timing of ERCP and success rate was not linear; thus, we categorized the timing of ERCP as a categorical variable. In our study, we attempted to identify a turning point and demonstrated that performing ERCP within this timeframe was more appropriate. The division at 3 days aligns with previous literature[9-11]. Viganò *et al*[25] found that the median time for the successful treatment of BDLs with an abdominal drainage tube was approximately 2 weeks, whereas drainage fluid exceeding 100 mL for more than 10 days (approximately 1 week) was associated with poor outcomes. Additionally, using a weekly division as a cutoff is more suitable for the observation period in clinical practice. Therefore, we chose weekly division as the cutoff point, categorizing the timing of ERCP into two binary variables.

The 21-day mark appears to be the turning point. The results showed that the success rate of ERCP for BDLs performed within 3 weeks was significantly higher than that for ERCP performed after 3 weeks. In addition, there were significantly fewer cases of biliary strictures if ERCP was performed within 3 weeks than if ERCP was performed after 3 weeks. We considered several factors that could influence outcomes, including the etiology and location of the BDL, the presence of abdominal drainage, laboratory test results, basic demographic characteristics, and the CCI. Potential confounders, such as liver transplant history, bile duct location, and preoperative laboratory values, were considered in the analysis of biliary strictures. To account for these confounding factors, we conducted univariate and multivariate analyses of the results, revealing that performing ERCP within 3 weeks was an independent factor for the success of ERCP and the lower incidence of biliary strictures. This may be attributed to prolonged bile stimulation, leading to infection, inflammation, and stenosis around the leakage site, which hinders the healing process. Further studies are required to validate these findings. Furthermore, cystic duct leakage was identified as a protective factor associated with ERCP success, which is consistent with previous research[31].

In 2021, the World Society of Emergency Surgery published guidelines for the management of bile duct injury during cholecystectomy[4]. They recommended that, for minor bile duct injuries, if no improvement or worsening of symptoms occurs during the clinical observation period after percutaneous drain placement, ERCP becomes mandatory. In cases of major bile duct injury diagnosed between 72 hours and 3 weeks, ERCP should be considered. Additionally, the acute inflammatory period typically requires several weeks (2-3 weeks) to resolve, making surgical treatment unsuitable within 3 weeks. This further emphasizes that ERCP performed within 3 weeks is a reasonable clinical management strategy.

Therefore, based on the guidelines and results of this study, we recommend that for patients diagnosed with BDLs, if there is abdominal drainage, it is advisable to initially observe. If there is no improvement in symptoms or signs or a decrease in drainage volume, ERCP can be performed. If there is improvement, re-evaluation can be done after 1-2 weeks. If there is no improvement or worsening of symptoms within 3 weeks, endoscopic management should be considered mandatory. These recommendations are summarized in Figure 1B. Our study has several limitations. First, the retrospective nature of the study introduced a potential bias in patient selection and data collection. Second, treatment preferences may have varied across centers, with some preferring nasobiliary drainage tubes and others opting for stents. However, both options have comparable efficacy; therefore, center preference is unlikely to significantly affect the results [7]. Third, the study did not include patients who underwent endoscopic sphincterotomy alone, as endoscopists at some centers believed that its clinical efficacy was relatively low, leading to surgical referrals[32].

CONCLUSION

Performing ERCP within 3 weeks may be associated with a higher success rate and lower incidence of biliary strictures. This finding highlights the significance of timely intervention in improving patient outcomes. When abdominal drainage does not improve within 3 weeks, early transition to ERCP is recommended. This facilitates better communication and collaboration between surgeons and endoscopists, ultimately benefiting the patients.

Table 1 Baseline characteristics of 94 patients with bile duct leaks, *n* (%)

Characteristics	Overall (*n* = 94)	< 3 weeks (*n* = 50)	> 3 weeks (*n* = 44)	*P* value
Basic demographics				
Sex	-	-	-	0.392
Female	28 (29.8)	13 (26)	15 (34.1)	-
Male	66 (70.2)	37 (74)	29 (65.9)	-
Age, years, mean ± SD	52.5 ± 12.9	54.1 ± 13.3	50.6 ± 12.4	0.192
BMI, mean ± SD	23.1 ± 3.4	23.1 ± 3.2	23.1 ± 3.7	0.830
CCI, (Q1, Q3)	3 (1, 4)	2 (1, 4)	3 (1, 5)	0.163
Laboratory test within 3 days before ERCP				
WBC, × 10^9/L (Q1, Q3)	8.2 (6.3, 16.9)	8.5 (7.2, 11.6)	8.1(6.0, 12.8)	0.909
ALT, U/L (Q1, Q3)	36.4 (25.9, 80.6)	32.3 (25.9, 57.3)	38 (24.7, 98.0)	0.480
Tbil, μmol/L (Q1, Q3)	20.2 (12.3, 38.8)	20.5 (13.5, 60.0)	18.5 (11.7, 36.5)	0.191
Albumin, g/L, mean ± SD	35.2 ± 5.9	35.4 ± 6.8	35.0 ± 4.8	0.728
Creatinine, μmol/L (Q1, Q3)	58.4 (48.9, 71.7)	57.2 (46.6, 71.1)	59.2 (46.4, 71.2)	0.796
Etiology of BDLs	-	-	-	0.307
Cholecystectomy	65 (69.1)	39 (78.0)	26 (59.1)	-
Liver transplantation	13 (13.8)	6 (12.0)	7 (15.9)	-
Partial hepatectomy	8 (8.5)	3 (6.0)	5 (11.4)	-
Trauma	4 (4.3)	1 (2.0)	3 (6.8)	-
Others	4 (4.3)	1 (2.0)	3 (6.8)	-
Treatment methods	-	-	-	0.149
Plastic stent	52 (55.3)	28 (56)	32 (64)	-
5 Fr	2 (2.1)	0 (0)	2 (4.5)	-
7 Fr	3 (3.2)	3 (6.0)	0 (0)	-
8.5 Fr	12 (12.8)	5 (10.0)	7 (15.9)	-
10 Fr	35 (37.2)	20 (40.0)	23 (52.3)	-
Metal stent (10 mm)	3 (3.2)	2 (4.0)	1 (2.3)	-
Nasobiliary drainage tube	31 (33.0)	20 (40.0)	11 (25.0)	-
Procedure characteristics				
Location of BDLs	-	-	-	0.488
Cystic duct	53 (56.4)	29 (58.0)	24 (54.5)	-
Common bile duct	20 (21.3)	10 (20.0)	10 (22.7)	-
Hilar bile duct	12 (12.8)	8 (16.0)	4 (9.1)	-
Intrahepatic bile duct	9 (9.6)	3 (6.0)	6 (13.6)	-
Abdominal drainage	76 (80.9)	42 (84.0)	34 (77.3)	0.410
Strasberg classification	-	-	-	0.259
A	38 (40.4)	24 (48.0)	14 (31.8)	-
C	11 (11.7)	5 (10.0)	6 (13.6)	-
D	32 (34.0)	13 (26.0)	19 (43.2)	-
E1	5 (5.3)	4 (8.0)	1 (2.3)	-
E2	8 (8.5)	4 (8.0)	4 (9.1)	-

ERCP: Endoscopic retrograde cholangiopancreatography; BDLs: Bile duct leaks; BMI: Body mass index; CCI: Charlson comorbidity index; WBC: White blood cell; ALT: Alanine aminotransferase; Tbil: Total bilirubin; Fr: French; Q1: First quartile; Q3: Third quartile.

Table 2 Success rate and biliary stricture associated with the timing of endoscopic retrograde cholangiopancreatography

Timing	Success (%)		OR	*P* value	Biliary stricture (%)		OR	*P* value
	Yes	No			Yes	No		
< 3, *n* = 6	5 (83.3)	1 (16.7)	0.946 (0.103-8.725)	0.961	2 (33.3)	4 (66.7)	0.130 (0.195-6.545)	0.892
> 3, *n* = 88	74 (84.1)	14 (15.9)	-	-	27 (30.7)	61 (69.3)	-	-
< 7, *n* = 18	16 (88.9)	2 (11.1)	1.651 (0.338-8.068)	0.536	3 (16.7)	15 (83.3)	0.385 (0.102-1.450)	0.158
> 7, *n* = 76	63 (82.9)	13 (17.1)	-	-	26 (34.2)	50 (65.8)	-	-
< 14, *n* = 32	28 (87.5)	4 (12.5)	1.510 (0.440-5.185)	0.513	4 (12.5)	28 (87.5)	0.211 (0.066-0.677)	0.009
> 14, *n* = 62	51 (82.3)	11 (17.7)	-	-	25 (40.3)	37 (59.7)	-	-
< 21, *n* = 50	46 (92.0)	4 (8.0)	3.833 (1.122-13.097)	0.032	9 (18.0)	41 (82.0)	0.263 (0.103-0.670)	0.005
> 21, *n* = 44	33 (75.0)	11 (25.0)	-	-	20 (45.5)	24 (54.5)	-	-

OR: Odds ratio.

Table 3 Univariable and multivariable analysis of factors associated with successful endoscopic retrograde cholangiopancreatography, *n* (%)

Variable	Univariable analysis			Multivariable analysis		
	Success (*n* = 79)	Failure (*n* = 15)	*P* value	OR	95%CI	*P* value
Basic demographics						
Sex, female	24 (30.4)	4 (26.7)	0.773	-	-	-
Age, years, mean ± SD	52.8 ± 12.7	51.0 ± 14.6	0.638	-	-	-
BMI, mean ± SD	23.4 ± 3.4	21.5 ± 3.1	0.049	0.814	0.653-1.014	0.067
CCI, (Q1, Q3)	2.5 (1, 4)	3.0 (2, 7)	0.031	0.864	0.704-1.062	0.164
Laboratory test within 3 days before ERCP						
WBC, × 10^9/L, mean ± SD	9.4 ± 4.3	10.4 ± 5.1	0.390	-	-	-
ALT, U/L (Q1, Q3)	36.1 (25.9, 81.2)	39.6 (22.8, 82.0)	0.812	-	-	-
Tbil, μmol/L (Q1, Q3)	19.3 (12.1, 39.4)	34.0 (12.6, 80.0)	0.715	-	-	-
Albumin, g/L, mean ± SD	35.3 ± 6.0	34.6 ± 5.6	0.659	-	-	-
Creatinine, μmol/L (Q1, Q3)	58.0 (47.0, 69.0)	59.3 (52.0, 99.0)	0.196	-	-	-
Etiology of BDLs	-	-	0.126	-	-	-
Cholecystectomy	58 (73.4)	7 (46.7)	-	-	-	-
Liver transplantation	9 (11.4)	4 (26.7)	-	-	-	-
Partial hepatectomy	7 (8.9)	1 (6.7)	-	-	-	-
Trauma	2 (2.5)	2 (13.3)	-	-	-	-
Others	3 (3.8)	1 (6.7)	-	-	-	-
Characteristics of different methods	--	-	0.326	-	-	-
Plastic stent	50 (63.3)	10 (66.7)	-	-	-	-
Metal stent (10 mm)	2 (2.5)	1 (6.7)	-	-	-	-
Nasobiliary drainage tube	27 (34.2)	4 (26.7)	-	-	-	-

Location of BDLs, cystic duct	51 (64.6)	2 (13.3)	0.002	12.219	2.317-64.433	0.003
Biliary stricture	23 (29.1)	6 (40.0)	0.403	-	-	-
Performing ERCP within 3 weeks	46 (58.2)	4 (26.7)	0.032	4.168	1.031-16.841	0.045
Abdominal drainage	64 (81.0)	12 (15.8)	0.938	-	-	-

OR: Odds ratio; CI: Confidence interval; ERCP: Endoscopic retrograde cholangiopancreatography; BMI: Body mass index; CCI: Charlson comorbidity index; WBC: White blood cell; ALT: Alanine aminotransferase; BDLs: Bile duct leaks; Tbil: Total bilirubin; Q1: First quartile; Q3: Third quartile.

Table 4 Univariable and multivariable analysis of variables associated with biliary stricture, *n* (%)

Variable	Univariable analysis			Multivariable analysis		
	Biliary stricture (*n* = 29)	No biliary stricture (*n* = 65)	*P* value	OR	95%CI	*P* value
Basic demographics						
Sex, female	12 (41.4)	16 (24.6)	0.104	-	-	-
Age, years, mean ± SD	54.14 ± 13.3	50.6 ± 12.39	0.585	-	-	-
BMI, mean ± SD	23.1 ± 3.2	23.1 ± 3.7	0.316	-	-	-
CCI, (Q1, Q3)	2 (1, 4)	3 (1, 5)	0.021	1.109	0.918-1.338	0.217
Laboratory test within 3 days before ERCP						
WBC, × 10^9/L (Q1, Q3)	8.4 (3, 4)	10.0 (4, 8)	0.110	-	-	-
ALT, U/L (Q1, Q3)	32.3 (25.9, 57.3)	38 (24.7, 98.0)	0.245	-	-	-
Tbil, μmol/L (Q1, Q3)	20.5 (13.5, 60.0)	18.6 (11.7, 36.5)	0.327	-	-	-
Albumin, g/L, mean ± SD	35.4 ± 6.8	35.0 ± 4.8	0.341	-	-	-
Creatinine, μmol/L (Q1, Q3)	57.2 (50.4, 73.8)	59.2 (46.4, 71.2)	0.916	-	-	-
Etiology of BDLs, liver transplantation	7 (24.1)	6 (9.2)	0.053	2.657	0.562-12.551	0.284
Location of BDLs	-	-	0.438	-	-	-
Cystic duct	14 (48.3)	39 (60.0)	-	-	-	-
Common bile duct	9 (31.0)	11 (16.9)	-	-	-	-
Hilar bile duct	4 (13.8)	8 (12.3)	-	-	-	-
Intrahepatic bile duct	2 (6.9)	7 (10.8)	-	-	-	-
Performing ERCP within 3 weeks	9 (31.0)	41 (63.1)	0.005	0.256	0.096-0.683	0.007

OR: Odds ratio; CI: Confidence interval; ERCP: Endoscopic retrograde cholangiopancreatography; BMI: Body mass index; CCI: Charlson comorbidity index; WBC: White blood cell; ALT: Alanine aminotransferase; BDLs: Bile duct leaks; Tbil: Total bilirubin; Q1: First quartile; Q3: Third quartile.

FOOTNOTES

Author contributions: Chen DX and Fang KX contributed to analysis, interpretation of data, drafting the article, they contributed equally to this article, they are the co-first authors of this manuscript; Chen SX, Hou SL, Wen GH, Yang HK, Shi DP, and Lu QX contributed to acquisition of data; Li MY is designated as the primary contact for all correspondence with the journal; Zhai YQ and Li MY contributed to revising, editing and drafting article, they contributed equally to this article, they are the co-corresponding authors of this manuscript; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Correlations of three scoring systems with the prognosis of patients with liver cirrhosis complicated with sepsis syndrome

Li-Nan Liu, Yu-Fei Chang, Hui Wang

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Abstract

BACKGROUND

Severe symptoms associated with sepsis syndrome (SS) are considered a severe threat, which not only increases therapeutic difficulty but also causes a prognostic mortality rate. However, at present, few related studies focused on the application of different score scales for disease and prognosis assessment in liver cirrhosis (LC) complicated with SS.

AIM

To determine the correlations of the model for end-stage liver disease (MELD), sequential organ failure assessment (SOFA), and modified early warning score (MEWS) points with the prognosis of patients with LC complicated with SS.

METHODS

This retrospective analysis included 426 LC cases from February 2019 to April 2022. Of them, 225 cases that were complicated with SS were assigned to the LC + SS group, and 201 simple LC cases were included in the LC group. Intergroup differences in MELD, SOFA, and MEWS scores were compared, as well as their diagnostic value for LC + SS. The correlations of the three scores with the prognosis of patients with LC + SS were further analyzed, as well as the related risk factors affecting patients' outcomes, after the follow-up investigation.

RESULTS

MELD, SOFA, and MEWS scores were all higher in the LC + SS group *vs* the LC group, and their combined assessment for LC + SS revealed a diagnostic sensitivity and a specificity of 89.66% and 90.84%, respectively ($P < 0.05$). The LC + SS group reported 58 deaths, with an overall mortality rate of 25.78%. Deceased patients presented higher MELD, SOFA, and MEWS points than those who survived ($P < 0.05$). MELD, SOFA, and MEWS scores were determined by COX analysis as factors independently affecting the prognosis of patients with LC + SS ($P < 0.05$).

CONCLUSION
MELD, SOFA, and MEWS effectively diagnosed LC in patients complicated with SS, and they demonstrated great significance in assessing prognosis, which provides a reliable prognosis guarantee for patients with LC + SS. However, their assessment effects remain limited, which is worthy of further investigation by more in-depth and rigorous experimental analysis.

Key Words: Model for end-stage liver disease; Sequential organ failure assessment; Modified early warning score; Cirrhosis; Sepsis syndrome

Core Tip: Severe symptoms and associated complications are crucial factors causing the death of patients with liver cirrhosis (LC). Among them, sepsis syndrome (SS) is a kind of severe threat, which not only increases therapeutic difficulty but also causes a prognostic mortality rate. This study confirmed the correlations of the model for end-stage liver disease, sequential organ failure assessment, and modified early warning score points with the prognosis of patients with LC complicated with SS.

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INTRODUCTION

Hepatitis, an extremely high-prevalence progressive disease globally, affects over 20 million patients in China alone[1], with > 5 million of them eventually progressing to life-threatening liver cirrhosis (LC)[2]. Alcohol addiction, obesity, hypertriglyceridemia, diabetes, overwork, and health products have been considered to trigger LC[3]. The early manifestations of LC are insidious and perceptually invisible. Hence, most patients are diagnosed in the middle or even late stage when they seek medical treatment. Severe symptoms and associated complications are crucial factors causing the death of patients with LC[4]. Decompensated LC, characterized by easy immune system damage and severe infection occurrence, is currently one of the most prevalent LC types[5,6]. Among them, sepsis syndrome (SS) is a type of severe threat, which not only increases therapeutic difficulty but also causes a prognostic mortality rate of > 70%[7,8]. Active prevention, detection, and active treatment of SS in patients with LC are the keys to reducing the case fatality rate, which has long been the focus of clinical research[9,10].

The model for end-stage liver disease (MELD) scoring system, which has been widely utilized in the diagnosis and treatment of liver diseases, effectively predicts the short- and medium-term mortality of end-stage liver diseases[11]. The sequential organ failure assessment (SOFA) score is one of the clinical scoring methods for critical disease severity. SOFA is objective, simple, easy to obtain, and reliable, with a high application frequency in SS[12]. The modified early warning score (MEWS) is a simple assessment system for disease and prognosis evaluation. MEWS quickly, simply, and scientifically scores the severity of the disease and then predicts the risk of patient death based on the comprehensive score of patients' heart rate, systolic blood pressure, respiratory rate, body temperature, and consciousness[13]. However, only a few related studies focused on the application of MELD, SOFA, and MEWS in LC complicated by SS (LC + SS) at present. This paper will provide a reliable theoretical basis for future clinical treatment by analyzing the correlation of the three scores with the prognosis of patients with LC + SS.

MATERIALS AND METHODS

General information

This study retrospectively analyzed 426 patients with LC who presented from February 2019 to April 2022, consisting of 225 patients with LC + SS (LC + SS group) and 201 cases with LC alone (LC group).

Eligibility criteria

All the enrolled cases present with clinical manifestations of LC and SS[14,15] and were diagnosed with LC (or LC + SS) after imaging and pathological assessment, with post-diagnosis treatment in our hospital, intact medical records, no adjuvant treatment before admission, and high compliance with the investigation work of our hospital. In contrast, those presenting with any of the following conditions were excluded from the study: Age of < 18 years; other tumors, or chronic, mental, or autoimmune diseases; hepatic and renal insufficiency; drug allergies; long-term bedridden and inability to take care of themselves due to physical disabilities; referrals; death during treatment.

Inspection methods

Body temperature, pulse, respiratory rate, *etc*., measurements were performed on all patients upon admission, and fasting venous blood (6 mL) was sampled for routine examinations, such as blood routine, liver function, and coagulation function, by the laboratory of our hospital. The assessment items included leukocytes, eosinophils, lymphocytes, C-reactive protein, procalcitonin (PCT), serum creatinine (SCr), uric acid, total bilirubin (TBiL), alanine transaminase (ALT), and aspartate aminotransferase (AST).

Scoring criteria

MELD was identified by referring to the MELD formula[16], namely, MELD = 3.8 × ln [TBiL (μmol/L)] × 0.059 + 11.2 × ln (international normalized ratio) + 9.6 × ln [SCr (μmol/L)] × 0.0113 + 6.4 × (0 for biliary or alcoholic LC, and 1 for others). SOFA score aimed to describe the occurrence and development of multiple organ dysfunction syndrome and assess the incidence, by recording the daily worst value, involving six organs, each with a score range of 0-4. The score was inversely correlated with the prognosis[17]. MEWS jointly evaluated the five physiological indicators of the patients, including consciousness, heart rate, body temperature, respiratory rate, and systolic blood pressure. Each item is scored 0-3, with the highest and lowest scores being 15 and 0 points, respectively[18].

Follow-up survey

The survival and mortality rates of patients during treatment and within one month after treatment completion were recorded.

Endpoints

Differences in MELD, SOFA, and MEWS were compared between the LC + SS group and the LC group, and the diagnostic value of the three for LC + SS was discussed. The correlations of the three scores with the prognosis of patients with LC + SS were further analyzed after the follow-up investigation, as well as the related risk factors affecting patient outcomes.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 23.0 was used for statistical data analysis. Gender and other count data were expressed as (%) and analyzed with a χ^2 test. The comparison was made by the independent sample *t*-test for quantitative data denoted by (mean ± SD). Diagnostic value was identified with receiver operating characteristic (ROC) curves. Binary Logistic regression analysis was conducted to obtain the joint value Log (*P*) for joint detection, after which ROC analysis was conducted. Related factors were determined with COX regression analysis. The presence of statistical significance was indicated with a *P* value of < 0.05.

RESULTS

Comparison of baseline data

We revealed no notable difference between the LC + SS group and the LC group when comparing age, sex, blood routine examination results, and other clinical baseline data between them ($P > 0.05$), indicating comparability (Table 1).

Comparison of MELD, SOFA, and MEWS

After investigation, MELD, SOFA, and MEWS of the LC + SS group were 18.93 ± 10.05, 6.32 ± 3.88, and 3.47 ± 1.94, respectively, all of which were lower as compared with the LC group of 15.23 ± 9.51, 4.98 ± 1.85, and 2.31 ± 1.33 ($P < 0.05$; Figure 1).

Effects of MELD, SOFA, and MEWS on predicting SS in patients with LC

ROC analysis revealed that the sensitivity and specificity for predicting SS in patients with LC were 75.56% and 42.29% in MELD of > 12.09 ($P < 0.05$), 31.56% and 93.53% in SOFA of > 7.50 ($P < 0.05$), and 94.22% and 27.36% in MEWS of > 1.50 ($P < 0.05$), respectively. A binary Logistic regression analysis was then conducted to obtain a joint detection formula of the three scores using MELD, SOFA, and MEWS as covariates, and whether the patient develops LC or not as the dependent variable: Log (*P*) = -1.718 + (0.038 × MELD) + (0.021 × SOFA) + (0.388 × MEWS). Subsequently, ROC analysis of Log (*P*) of the two groups revealed that the sensitivity and specificity for predicting SS in patients with LC were 33.78% and 93.03%, respectively, in Log (*P*) of > 0.68 ($P < 0.05$; Figure 2).

Evaluation effect of MELD, SOFA, and MEWS on prognosis

The LC + SS group reported 58 deaths, with an overall mortality rate of 25.78%. Cases were further assigned to either the dead or the surviving group based on their survival. Inter-group comparisons of MELD, SOFA, and MEWS revealed higher scores in the dead group *vs* the surviving group ($P < 0.05$). Subsequently, ROC analysis was conducted, indicating sensitivity and specificity for predicting patient death of 84.48% and 79.04% in MDLD of > 19.91 ($P < 0.05$), 86.20% and 81.44% in SOFA of > 6.50 ($P < 0.05$), and 68.97% and 73.65% in MDLD of > 3.50 ($P < 0.05$), respectively. While the Log (*P*) = -4.906 + (0.064 × MELD) + (0.364 × SOFA) + (-0.053 × MEWS) of the combined tests of the threescores demonstrated a sensitivity of 89.66% and a specificity of 90.84% in predicting patient death ($P < 0.05$; Figure 3).

Table 1 Comparison of baseline data

	LC group (*n* = 201)	LC + SS group (*n* = 225)	*t*/χ^2	*P* value
Age (years)	55.08 ± 12.10	54.92 ± 12.29	0.135	0.893
Body temperature (°C)	37.59 ± 1.13	37.60 ± 1.08	0.093	0.926
The pulse (times/minutes)	94.60 ± 16.47	95.67 ± 17.45	0.649	0.517
Respiratory rate (times/minutes)	20.94 ± 4.06	21.08 ± 4.05	0.356	0.722
White blood cells (× 10^9/L)	10.22 ± 6.52	9.60 ± 7.62	0.897	0.370
Neutrophils (× 10^9/L)	9.70 ± 6.19	8.46 ± 8.78	1.666	0.096
Eosinophils (%)	0.05 ± 0.04	0.04 ± 0.07	1.782	0.076
Lymphocytes (× 10^9/L)	0.97 ± 0.72	0.90 ± 0.99	0.826	0.409
Hb (g/L)	96.44 ± 22.96	96.19 ± 27.59	0.101	0.920
PLT (× 10^9/L)	86.39 ± 58.82	82.08 ± 73.73	0.662	0.509
Gender			1.319	0.251
Male/female	141/60	169/56		
Smoking history			1.267	0.260
Yes/no	45/156	61/164		
Alcohol consumption history			1.531	0.216
Yes/no	67/134	88/137		
Body mass index (kg/m^2)	23.36 ± 3.25	23.12 ± 3.18	0.770	0.442
Diabetes	47/154	65/160	1.661	0.198
Hypertension	53/148	68/157	0.775	0.379

Hb: Hemoglobin; PLT: Platelets; LC: Liver cirrhosis; SS: Sepsis syndrome.

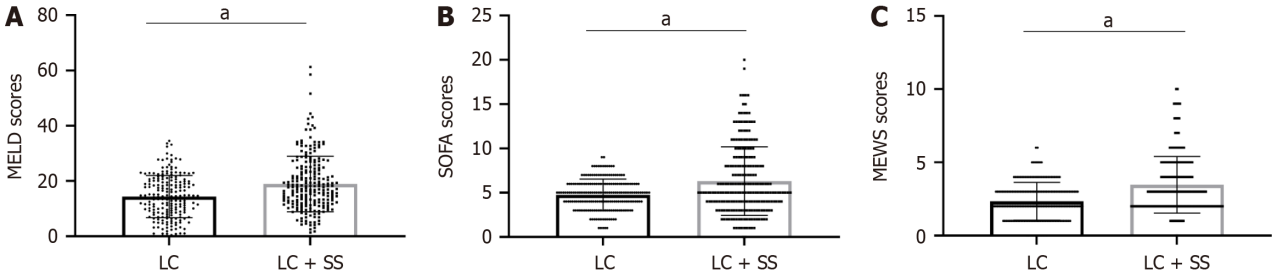

Figure 1 Comparison of model for end-stage liver disease, sequential organ failure assessment and modified early warning scores. A: Comparison of model for end-stage liver disease (MELD) scores between liver cirrhosis (LC) + sepsis syndrome (SS) group and LC group; B: Comparison of sequential organ failure assessment scores between LC + SS group and LC group; C: Comparison of modified early warning scores between LC + SS group and LC group. $^aP < 0.05$; MELD: End-stage liver disease; SOFA: Sequential organ failure assessment; MEWS: Modified early warning score; LC: Liver cirrhosis; SS: Sepsis syndrome.

Univariate analysis of prognosis in patients with LC + SS

Univariate analysis revealed no statistical difference in age, gender, *etc.*, between groups ($P > 0.05$), indicating that none of the above indicators were single factors affecting the prognosis of patients with LC + SS. However, higher white blood cells, pulse, TBiL, *etc.*, were identified in the dead group compared with the surviving group, with lower respiratory rate, PTA, *etc.*, than the survival group ($P < 0.05$), indicating the role of these scores as single factors affecting outcomes of patients with LC + SS (Table 2).

Multivariate analysis of prognosis in patients with LC + SS

The univariate indexes in the above analysis were assigned and input into SPSS for multivariate COX analysis. MELD, SOFA, MEWS, PCT, presence of chronic liver failure, acute liver failure, acute renal failure, respiratory failure, acute heart failure, and septic shock ($P < 0.05$) were considered independent factors affecting the prognosis of patients with LC + SS but not age, body temperature, respiratory rate, *etc.*, ($P > 0.05$; Tables 3 and 4).

Table 2 Univariate analysis of prognosis in liver cirrhosis + sepsis syndrome patients

	Surviving patient (*n* = 167)	Dead patients (*n* = 58)	t/χ^2	*P* value
Age (years)	53.58 ± 12.32	58.76 ± 11.46	2.807	0.005
Body temperature (°C)	37.75 ± 1.09	37.19 ± 0.96	3.472	< 0.001
The pulse (times/minute)	93.20 ± 17.13	102.79 ± 16.46	3.710	< 0.001
Respiratory rate (times/minute)	20.29 ± 2.88	23.36 ± 5.77	5.256	< 0.001
White blood cells ($\times 10^9$/L)	8.55 ± 6.97	12.60 ± 8.62	3.578	< 0.001
Neutrophils ($\times 10^9$/L)	7.61 ± 8.91	10.89 ± 7.95	2.481	0.014
Eosinophils (%)	0.05 ± 0.07	0.03 ± 0.06	1.942	0.053
Lymphocytes ($\times 10^9$/L)	0.86 ± 0.93	1.01 ± 1.14	0.996	0.320
Hb (g/L)	96.79 ± 27.74	94.43 ± 27.33	0.560	0.576
PLT ($\times 10^9$/L)	82.00 ± 77.24	82.07 ± 63.14	0.006	0.995
PCT (ng/L)	11.27 ± 5.40	19.39 ± 31.37	3.223	0.002
CRP (mg/L)	57.55 ± 65.80	75.74 ± 63.35	1.831	0.068
LaC (mmol/L)	2.67 ± 2.42	6.08 ± 4.07	7.632	< 0.001
ALT (U/L)	40.60 ± 100.66	188.87 ± 511.08	3.569	< 0.001
AST (U/L)	75.66 ± 273.75	344.20 ± 898.21	3.442	< 0.001
ALB (g/L)	29.99 ± 5.20	27.55 ± 6.18	2.928	0.004
TBiL (μmol/L)	78.35 ± 93.75	166.86 ± 139.29	5.415	< 0.001
PTA (%)	54.58 ± 18.71	33.35 ± 17.58	7.559	< 0.001
Creatinine (μmol/L)	94.31 ± 71.71	215.54 ± 265.12	5.388	< 0.001
Gender			0.304	0.581
Male/female	127/40	42/16		
Liver cancer			1.364	0.243
None/have	129/38	49/9		
Hypertension			6.224	0.013
None/have	136/31	38/20		
Diabetes			3.777	0.052
None/have	138/29	41/17		
Coronary heart disease			9.068	0.003
None/have	159/8	48/10		
Chronic renal insufficiency			7.822	0.005
None/have	158/9	48/10		
Chronic liver failure			47.640	< 0.001
None/have	116/51	10/48		
Acute liver failure			59.900	< 0.001
None/have	151/16	24/34		
Acute renal failure			81.780	< 0.001
None/have	138/29	10/48		
Respiratory failure			67.210	< 0.001
None/have	160/7	29/29		
Acute heart failure			28.090	< 0.001
None/have	161/6	42/16		

Septic shock			115.900	< 0.001
None/have	144/23	5/53		
Hepatic encephalopathy			47.600	< 0.001
None/have	136/31	19/39		
Upper gastrointestinal bleeding			6.939	0.008
None/have	128/39	34/24		

Hb: Hemoglobin; PLT: Platelets; PCT: Procalcitonin; CRP: C-reactive protein; LAC: Blood lactate; ALT: Alanine transaminase; AST: Aspartate transaminase; ALB: Plasma albumin; TBiL: Total bilirubin; PTA: Prothrombin activity.

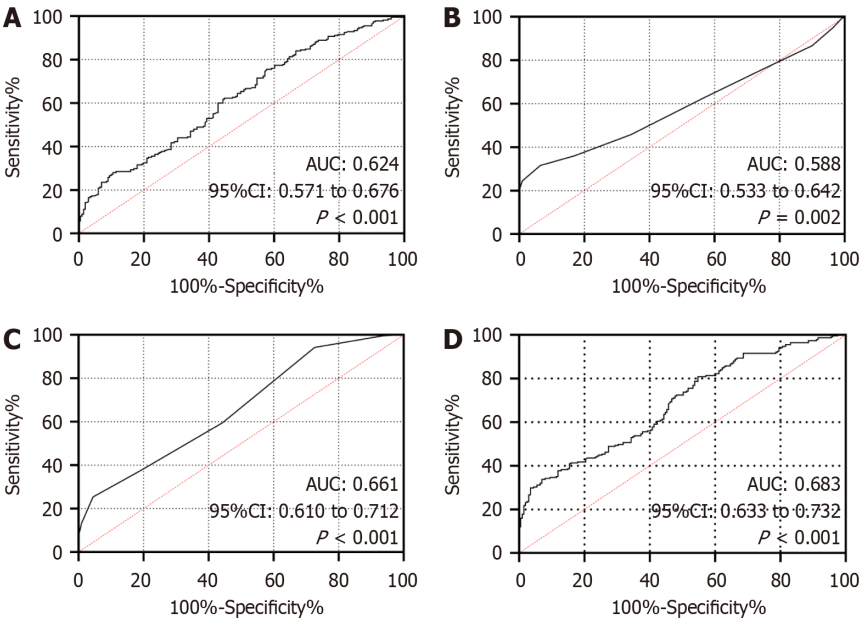

Figure 2 Impacts of model for end-stage liver disease, sequential organ failure assessment and modified early warning scores on predicting sepsis syndrome in liver cirrhosis patients. A: Receiver operating characteristic (ROC) curve of model for end-stage liver disease (MELD) for predicting sepsis syndrome (SS) in liver cirrhosis (LC) patients; B: ROC curve of sequential organ failure assessment (SOFA) for predicting SS in LC patients; C: ROC curve of modified early warning score (MEWS) for predicting SS in LC patients; D: ROC curve of MELD, SOFA and MEWS combined for predicting SS in LC patients. AUC: Area under curve; LC: Liver cirrhosis; SS: Sepsis syndrome.

DISCUSSION

At present, an independent scoring system to predict the prognosis of patients co-infected with LC with infection remains lacking. The correlation of MELD, SOFA, and MEWS with LC or other organ failure has been repeatedly verified[19-21], but their employment in LC + SS assessment remains rare. Therefore, this study demonstrates important reference significance for future clinical prevention of SS and prognosis evaluation of patients by investigating the correlation of MELD, SOFA, and MEWS with LC + SS.

This study first conducted inter-group comparisons in terms of MELD, SOFA, and MEWS. It revealed higher MELD, SOFA, and MEWS in the LC + SS group than in the LC group, indicating a certain correlation between the three scores and SS in patients with LC. Patients with LC generally present with multi-organ functional disturbance and multiple organ failure. Additionally, infection is the leading cause of complications as well as the primary reason for death, thereby significantly increasing the mortality of co-infected patients[22]. The prognosis judgment of infection involves not only the liver itself and the disease state but also the degree of infection. Therefore, early warning, as well as early diagnosis and intervention, which have always been a hot issue, are crucial[23,24]. In this study, we conducted ROC analysis and revealed that the MELD, SOFA, and MEWS were all of favorable diagnostic value in diagnosing LC in patient with SS, with the sensitivity and specificity of their combined tests being 89.66% and 90.84%, respectively, which has extremely important reference significance for LC + SS that lacks effective assessment scheme at present. Furthermore, the three scores were considered factors that independently affect the prognosis of patients with LC + SS in the follow-up of prognosis. The prognostic survival curve and ROC indicate that the three scores demonstrated good diagnostic value for prognostic death, with their increased assessment results, exhibiting an increased risk of death in patients. Therefore, in the future, MELD, SOFA, and MEWS are expected to effectively assess the prognosis of patients with LC + SS in an early stage to enable timely intervention, thereby providing a more reliable guarantee for improving

Table 3 Assignment table

Factors	Assign
Age (years)	Use raw data for analysis
Body temperature (°C)	Use raw data for analysis
The pulse (times/minute)	Use raw data for analysis
Respiratory rate (times/minute)	Use raw data for analysis
White blood cells ($\times 10^9$/L)	Use raw data for analysis
Neutrophils ($\times 10^9$/L)	Use raw data for analysis
PCT (ng/L)	Use raw data for analysis
LaC (mmol/L)	Use raw data for analysis
ALT (U/L)	Use raw data for analysis
AST (U/L)	Use raw data for analysis
ALB (g/L)	Use raw data for analysis
TBiL (μmol/L)	Use raw data for analysis
PTA (%)	Use raw data for analysis
Creatinine (μmol/L)	Use raw data for analysis
MELD scores	Use raw data for analysis
SOFA scores	Use raw data for analysis
MEWS scores	Use raw data for analysis
Hypertension	None assignment is "0", have assignment is "1"
Coronary heart disease	None assignment is "0", have assignment is "1"
Chronic renal insufficiency	None assignment is "0", have assignment is "1"
Chronic liver failure	None assignment is "0", have assignment is "1"
Acute liver failure	None assignment is "0", have assignment is "1"
Acute renal failure	None assignment is "0", have assignment is "1"
Respiratory failure	None assignment is "0", have assignment is "1"
Acute heart failure	None assignment is "0", have assignment is "1"
Septic shock	None assignment is "0", have assignment is "1"
Hepatic encephalopathy	None assignment is "0", have assignment is "1"
Upper gastrointestinal bleeding	None assignment is "0", have assignment is "1"

PCT: Procalcitonin; LaC: Blood lactate; ALT: Alanine transaminase; AST: Aspartate transaminase; ALB: Plasma albumin; TBiL: Total bilirubin; PTA: Prothrombin activity; MELD: End-stage liver disease; SOFA: Sequential organ failure assessment; MEWS: Modified early warning score.

patient outcomes. Previous studies[25-28] revealed a single scoring scale to have some clinical application value. In particular, individual SOFA component predictors were useful in identifying in-hospital mortality or prolonged intensive care unit stay, which may help determine a subset of patients with sepsis who are at increased risk for adverse outcomes. More importantly, the results indicate that individual SOFA components, although independently related to outcomes, do not exhibit similar predictive power for all organ dysfunction[26]. The MEWS has been considered a reliable and easy-to-use first-time patient assessment score. It helps in the management of patients before and during hospitalization[27]. However, these previous studies were all focused on a single scale. In contrast to our study, we have combined the three scales, although we also revealed that the evaluation based on the three scores demonstrated the following limitations: (1) The three scores are too subjective, which may cause misdiagnosis and missed diagnosis; (2) Multiple organ failure and other basic diseases are prevalent in patients with LC + SS, and MELD, SOFA, and MEWS scores may be influenced by other factors, causing a final result not so specific for SS assessment; and (3) Detailed segmentation of score results remains lacking, causing large differences in prognosis among patients with consistent scoring results. Given the above, much room for improvement remains in the assessment of LC + SS by MELD, SOFA, and MEWS in the future. In particular, the weight of each score can be increased, more detailed evaluation criteria can be developed for the pathological manifestations of LC, and some objective indicators can be added to assist in assessing disease progression.

Table 4 Multivariate analysis of prognosis in liver cirrhosis + sepsis syndrome patients

Factors	B	SE	χ^2	*P* value	OR	95%CI
Age (years)	0.225	0.114	3.942	> 0.05	1.241	1.010-1.562
Body temperature (°C)	0.342	0.263	1.714	> 0.05	1.415	0.842-2.364
The pulse (times/minute)	0.169	0.315	0.281	> 0.05	1.180	0.634-2.094
Respiratory rate (times/minute)	0.442	0.216	4.062	> 0.05	1.612	1.031-2.424
White blood cells ($\times 10^9$/L)	0.176	0.311	0.342	> 0.05	1.194	0.642-2.191
Neutrophils ($\times 10^9$/L)	0.323	0.164	4.061	> 0.05	1.394	1.004-1.924
PCT (ng/L)	0.340	0.142	5.584	< 0.05	1.401	1.061-1.867
LaC (mmol/L)	0.226	0.114	3.984	> 0.05	1.264	1.001-1.569
ALT (U/L)	1.642	0.342	3.032	> 0.05	4.061	1.942-8.662
AST (U/L)	0.681	0.406	2.716	> 0.05	1.942	0.884-4.621
ALB (g/L)	1.031	0.384	3.621	> 0.05	2.841	1.334-6.256
TBiL (μmol/L)	0.122	0.064	4.103	> 0.05	1.421	1.224-1.618
PTA (%)	0.143	0.043	6.262	> 0.05	1.246	1.081-2.621
Creatinine (μmol/L)	0.257	0.041	3.627	> 0.05	1.581	1.413-2.782
MELD scores	0.327	0.034	46.121	< 0.001	1.815	1.224-2.493
SOFA scores	-0.218	0.036	34.861	< 0.001	1.712	1.344-2.483
MEWS scores	0.912	0.196	24.312	< 0.001	2.493	1.731-3.562
Hypertension	0.612	0.241	4.311	> 0.05	1.814	1.184-2.886
Coronary heart disease	0.381	0.181	4.371	> 0.05	1.460	1.013-2.262
Chronic renal insufficiency	0.348	0.181	3.861	> 0.05	1.693	1.482-1.983
Chronic liver failure	-0.651	0.191	17.593	< 0.001	1.51	1.340-1.798
Acute liver failure	0.284	0.114	6.412	0.010	1.381	1.068-1.663
Acute renal failure	3.816	0.342	70.161	< 0.001	27.062	12.811-60.347
Respiratory failure	-0.421	0.192	15.010	< 0.001	1.663	1.452-2.958
Acute heart failure	0.263	0.234	10.068	< 0.001	1.061	1.020-1.683
Septic shock	0.623	0.172	35.061	< 0.001	1.527	1.384-1.730
Hepatic encephalopathy	-0.311	0.142	4.621	> 0.05	0.721	0.516-0.972
Upper gastrointestinal bleeding	0.612	0.172	3.284	> 0.05	1.554	1.396-1.768

PCT: Procalcitonin; LaC: Blood lactate; ALT: Alanine transaminase; AST: Aspartate transaminase; ALB: Plasma albumin; TBiL: Total bilirubin; PTA: Prothrombin activity; MELD: End-stage liver disease; SOFA: Sequential organ failure assessment; MEWS: Modified early warning score; OR: Odds ratio.

This study has many limitations to be addressed. First, this is a retrospective analysis with a limited number of cases; thus, some errors are unavoidable. Second, as aforementioned, we need to screen the selected cases and reduce other factors that may affect the scoring results (such as other organ failure) to improve the accuracy of the experimental results. Third, patients with LC with other complications were not included in the sample to observe whether the presence of other complications would affect the prediction accuracy. Fourth, the sample size of the study was too small to further verify the current conclusion due to the retrospective and single-center study design. Finally, we need to follow up with the patients for a longer time to further analyze the assessment effect of MELD, SOFA, and MEWS on patients' long-term prognosis. Therefore, a well-designed, large sample size, multi-center with long-term follow-up study is warranted for further investigation.

CONCLUSION

Collectively, MELD, SOFA, and MEWS effectively diagnose patients with LC complicated with SS and play an excellent role in assessing the prognosis of patients, thereby providing reliable prognosis guarantee for patients with LC + SS.

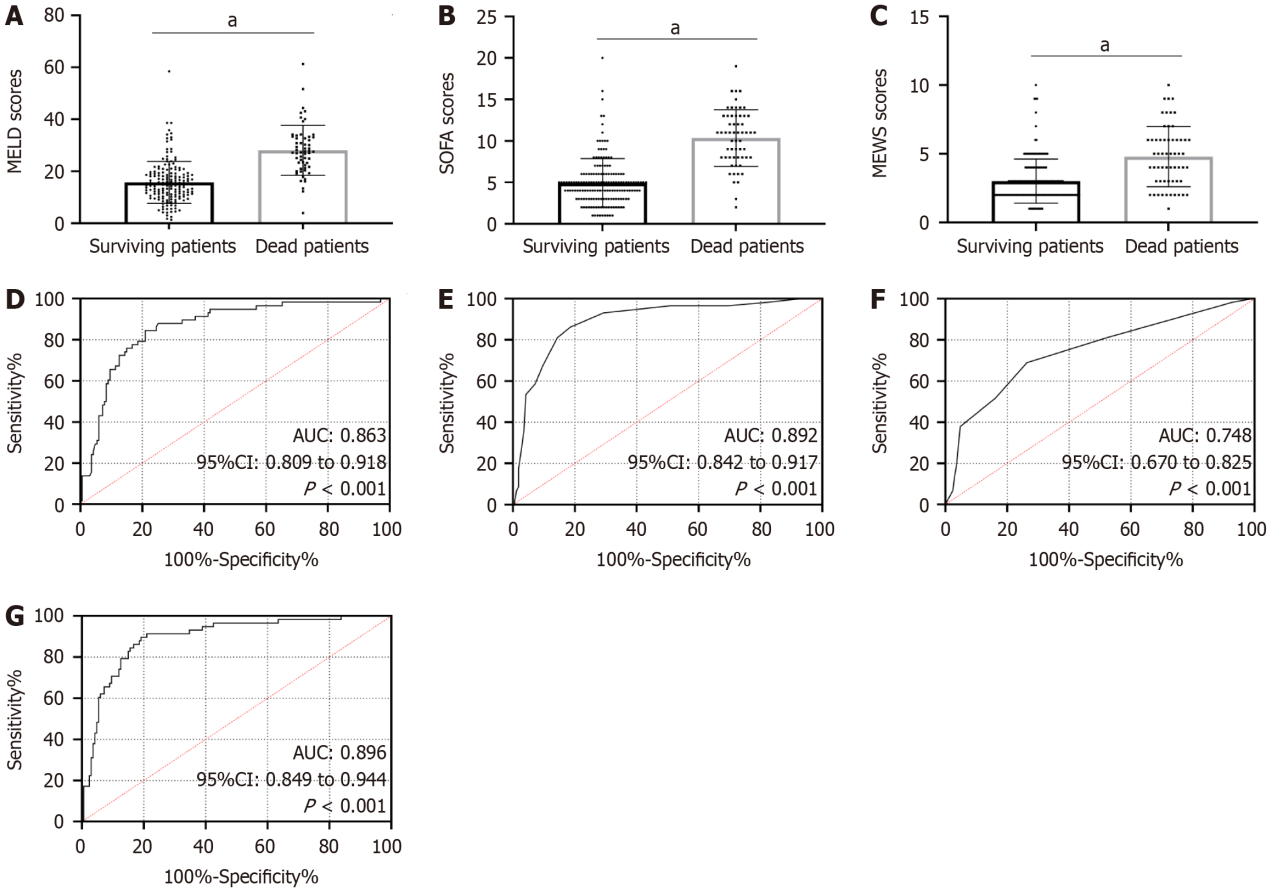

Figure 3 Evaluation effect of model for end-stage liver disease, sequential organ failure assessment and modified early warning scores on prognosis. A: Comparison of model for end-stage liver disease (MELD) scores between dead patients and surviving patient; B: Comparison of sequential organ failure assessment (SOFA) scores between dead patients and surviving patient; C: Comparison of modified early warning score (MEWS) between dead patients and surviving patient; D: Receiver operating characteristic (ROC) curve of MELD in predicting the death of liver cirrhosis (LC) patients with sepsis syndrome (SS); E: ROC curve of SOFA in predicting the death of LC patients with SS; F: ROC curve of MEWS in predicting the death of LC patients with SS; G: ROC curve of MELD, SOFA and MEWS combined in predicting the death of LC patients with SS. $^{a}P < 0.05$; MELD: End-stage liver disease; SOFA: Sequential organ failure assessment; MEWS: Modified early warning score; LC: Liver cirrhosis; SS: Sepsis syndrome.

However, their evaluation effects still have some limitations, which is worthy of further investigation by more in-depth and rigorous experimental analysis.

FOOTNOTES

Author contributions: Liu LN designed the study, collected and analyzed data, and wrote the manuscript; Liu LN, Chang YF and Wang H participated in the study's conception and data collection; Liu LN and Wang H participated in study design and provided guidance; All authors read and approved the final version.

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ORIGINAL ARTICLE

Retrospective Study

Analgesic effect and safety of dexmedetomidine-assisted intravenous-inhalation combined general anesthesia in laparoscopic minimally invasive inguinal hernia surgery

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Abstract

BACKGROUND

Currently, very few studies have examined the analgesic effectiveness and safety of dexmedetomidine-assisted intravenous-inhalation combined general anesthesia in laparoscopic minimally invasive surgery for inguinal hernia.

AIM

To investigate the analgesic effect and safety of dexmedetomidine-assisted intravenous-inhalation combined general anesthesia in laparoscopic minimally invasive surgery for inguinal hernia.

METHODS

In this retrospective study, 94 patients scheduled for laparoscopic minimally invasive surgery for inguinal hernia, admitted to Yiwu Central Hospital between May 2022 and May 2023, were divided into a control group (inhalation combined general anesthesia) and a treatment group (dexmedetomidine-assisted intravenous-inhalation combined general anesthesia). Perioperative indicators, analgesic effect, preoperative and postoperative 24-hours blood pressure (BP) and heart rate (HR), stress indicators, immune function levels, and adverse reactions were compared between the two groups.

RESULTS

Baseline data, including age, hernia location, place of residence, weight, monthly income, education level, and underlying diseases, were not significantly different between the two groups, indicating comparability ($P > 0.05$). No significant difference was found in operation time and anesthesia time between the two

groups ($P > 0.05$). However, the treatment group exhibited a shorter postoperative urinary catheter removal time and hospital stay than the control group ($P < 0.05$). Preoperatively, no significant differences were found in the visual analog scale (VAS) scores between the two groups ($P > 0.05$). However, at 12, 18, and 24 hours postoperatively, the treatment group had significantly lower VAS scores than the control group ($P < 0.05$). Although no significant differences in preoperative hemodynamic indicators were found between the two groups ($P > 0.05$), both groups experienced some extent of changes in postoperative HR, diastolic BP (DBP), and systolic BP (SBP). Nevertheless, the treatment group showed smaller changes in HR, DBP, and SBP than the control group ($P < 0.05$). Preoperative immune function indicators showed no significant differences between the two groups ($P > 0.05$). However, postoperatively, the treatment group demonstrated higher levels of $CD3^+$, $CD4^+$, and $CD4+/CD8^+$ and lower levels of $CD8^+$ than the control group ($P < 0.05$). The rates of adverse reactions were 6.38% and 23.40% in the treatment and control groups, respectively, revealing a significant difference ($\chi^2 = 5.371$, $P = 0.020$).

CONCLUSION

Dexmedetomidine-assisted intravenous-inhalation combined general anesthesia can promote early recovery of patients undergoing laparoscopic minimally invasive surgery for inguinal hernia. It ensures stable blood flow, improves postoperative analgesic effects, reduces postoperative pain intensity, alleviates stress response, improves immune function, facilitates anesthesia recovery, and enhances safety.

Key Words: Dexmedetomidine; Intravenous-inhalation combined general anesthesia; Inguinal hernia; Laparoscopic minimally invasive surgery; Analgesia; Safety

Core Tip: This study aimed to assess the analgesic effect and safety of dexmedetomidine-assisted intravenous-inhalation combined general anesthesia in laparoscopic minimally invasive surgery for inguinal hernia through systematic clinical observation and analysis. The study enrolled a total of 94 patients with inguinal hernia who were scheduled to undergo laparoscopic minimally invasive surgery. Comparative analyses were performed on the clinical outcomes between inhalation anesthesia combined with general anesthesia and dexmedetomidine-assisted intravenous-inhalation combined general anesthesia in these patients. The results revealed that dexmedetomidine-assisted intravenous-inhalation combined general anesthesia can facilitate the early recovery of patients undergoing laparoscopic minimally invasive surgery for inguinal hernia, ensure hemodynamic stability, enhance postoperative analgesic effects, alleviate stress response, and improve immune function while exhibiting a certain safety level.

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INTRODUCTION

Inguinal hernia is a common abdominal wall disease and accounts for 85%-95% of all hernia cases. Traditional treatment methods, including hernia repair surgery and open surgery, are associated with significant postoperative pain, extensive trauma, and longer recovery period[1,2]. As medical technology advances, laparoscopic minimally invasive surgery has increasingly become the preferred treatment option for inguinal hernia[3]. However, postoperative pain remains a significant clinical issue in laparoscopic minimally invasive surgery, which affects patients' postoperative comfort and recovery quality[4]. Currently, traditional anesthesia modalities employed in inguinal hernia surgeries present several deficiencies, including inadequate preservation of hemodynamic stability, limited postoperative analgesic efficacy, and high propensity for adverse reactions[5,6]. Consequently, an exploratory optimization endeavor regarding the anesthesia protocol for inguinal hernia surgeries is imperative. In recent years, dexmedetomidine has been widely used as an adjunct analgesic medication to improve postoperative analgesic effects and enhance surgical safety in clinical anesthesia practice. Dexmedetomidine, a selective α2-adrenergic receptor agonist[7], possesses analgesic, sedative, and anxiolytic properties. It effectively alleviates postoperative pain, promotes patient sedation, and minimizes the need for analgesic medications during and after surgery. Currently, research on the analgesic effect and safety of dexmedetomidine-assisted inhalation anesthesia in laparoscopic minimally invasive surgery for inguinal hernia is relatively scarce. Therefore, this study aimed to evaluate the analgesic effect and safety of dexmedetomidine-assisted inhalation anesthesia in laparoscopic minimally invasive surgery for inguinal hernia through systematic clinical observation and analysis.

MATERIALS AND METHODS

General information

This retrospective study included 94 patients with inguinal hernia scheduled for laparoscopic minimally invasive surgery, who were admitted to Yiwu Central Hospital between May 2022 and May 2023. The patients were allocated into a control group and a treatment group, with 47 patients in each group. The inclusion criteria were as follows: (1) Diagnosis of inguinal hernia confirmed through clinical examination and other necessary imaging studies[8]: Presence of protrusion or bulge in the inguinal region with discomfort or pain; palpable mass or bulge in the groin area, which becomes more prominent during activities such as coughing, exertion, or standing; (2) American Society of Anesthesiologists physical status classification of grades I–II[9]; (3) No history of drug allergies; (4) General surgical tolerance without severe cardiovascular, pulmonary, or other systemic diseases; (5) No contraindications, such as severe coagulation disorders, hepatic or renal insufficiency, and advanced malignant tumors; and (6) Complete clinical data. The exclusion criteria were as follows: (1) Severe cardiovascular diseases, such as severe heart failure and myocardial infarction; (2) Severe respiratory diseases, such as severe chronic obstructive pulmonary disease and respiratory failure; (3) Coagulation disorders, such as severe blood coagulation disorders or inability to adjust anticoagulant treatment; (4) Severe hepatic or renal dysfunction, such as advanced liver cirrhosis and renal failure; (5) Malignant tumors, such as advanced malignant tumors and metastatic tumors; (6) Prior or intraoperative use of other analgesic medications, or severe immunodeficiency, such as human immunodeficiency virus infection and postorgan transplant; (7) Use of other medications for treatment; and (8) Inability to contact the patients during the follow-up period due to changes in address or telephone number. Table 1 presents the baseline characteristics of the two patient groups.

Treatment methods

Preoperatively, patients underwent bowel and bladder preparation. They were then transferred to the operating room and subjected to routine monitoring, including arterial pressure monitoring and establishing a vein access for intravenous administration. Various monitoring devices were connected to comprehensively monitor patients' vital signs. Anesthesia was induced, and sedative medications, such as midazolam, were administered to alleviate anxiety and pain.

In the control group, anesthesia induction involved intravenous administration of propofol, cisatracurium besylate, and sufentanil for endotracheal intubation, followed by the inhalation of 2.5%-4.5% sevoflurane (Lunan Better Pharmaceutical Co., Ltd. H20080681, 100 mL). In the treatment group, in addition to the medications used in the control group, patients were administered dexmedetomidine at a dose of 1.0 μg/kg (Yangtze River Pharmaceutical Group, Jiangsu, China, H20183219, 2 mL/0.2 mg), prepared at a concentration of 4 μg/mL. The dose of 1 μg/kg was administered *via* slow intravenous infusion over a period of more than 10 minutes. The dose was adjusted based on the patient's condition. After anesthesia induction, endotracheal intubation was performed to connect the airway to the ventilator, ensuring adequate ventilation and oxygenation of the patient. During the anesthesia procedure, vital signs [blood pressure (BP), heart rate (HR), and respiration] were monitored, and the anesthetic agent was adjusted as necessary to maintain the depth of anesthesia and stable physiological state. Once a stable anesthesia state was reached, under laparoscopic guidance, the surgeon inserted a laparoscope and surgical instruments through small incisions to perform hernia repair. After the procedure, the surgical area was examined to ensure no bleeding or residual hernia sac. The incision was sutured, dressings were applied, and the anesthetic agent was discontinued.

Observation indicators

Surgical time, anesthesia time, postoperative urinary catheter removal time, and length of hospital stay were recorded for both groups. Pain scores in both groups were recorded before surgery and at 12, 18, and 24 hours after surgery using the visual analog scale (VAS) scoring criteria[10]. The VAS scores range from 0 to 10 points, where 0 represents no pain, < 3 indicate mild pain within the patient's tolerance, 4-6 indicate moderate pain that affects sleep, and 7-10 indicate severe pain beyond the patient's tolerance.

Hemodynamics: The HR, diastolic BP (DBP), systolic BP (SBP), and other indicators were measured before surgery and immediately after surgery.

Stress indicator test: In this study, 5 mL of peripheral venous blood was collected before surgery and 24 hours after surgery. The blood samples were centrifuged for 15 minutes using a KDC-2046 Low-speed centrifuge (Anhui Zhongkejia Scientific Instrument Co. Ltd.) to separate the serum. Cortisol, adrenaline, and noradrenaline levels were measured using enzyme-linked immunoassay (ELISA) kits (Shanghai Jianglai Biotechnology Co. Ltd.). The measurements were performed using an AP-960 fully automatic ELISA analyzer (Japan Kyowa Pharmaceutical Co. Ltd.), following the provided kit instructions.

Immune function: Peripheral venous blood (4 mL, anticoagulated with heparin) was extracted before and after surgery. The blood samples were centrifuged to separate the leukocyte layer. The percentages of lymphocyte subsets were calculated using a FACSCanto flow cytometer (BD Company, United States) and a three-color flow cytometry assay. Reagent kits for the detection of T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$) were provided by Beckman Coulter (United States).

Postoperative adverse reactions, including dizziness, nausea, vomiting, dry mouth, and incision infection, were recorded and compared between the two groups. The follow-up period was from May 20, 2023, to June 20, 2023, with all patients receiving follow-up.

Statistical analysis

For quantitative data (including age, body weight, perioperative indicators, VAS scores, hemodynamic indicators, stress

Table 1 Comparison of basic patient characteristics between the two groups

Projects		Control group (n = 47)	Treatment group (n = 47)	t/χ^2	P value
Age (years)		48.06 ± 6.58	48.13 ± 6.62	0.051	0.959
Hiatal hernia site (left/right)		29/18	27/20	0.177	0.674
Place of residence (urban/rural)		25/22	24/23	0.043	0.836
Body weight (kg)		67.51 ± 10.68	68.05 ± 10.72	0.245	0.807
Monthly household income (> 2000 RMB/≤ 2000 RMB)		24/23	26/21	0.171	0.679
Academic status (college and below/bachelor and above)		21/26	20/27	0.043	0.835
Underlying disease (cases)	High blood pressure	6	5	0.103	0.748
	Diabetes	3	5	0.547	0.460

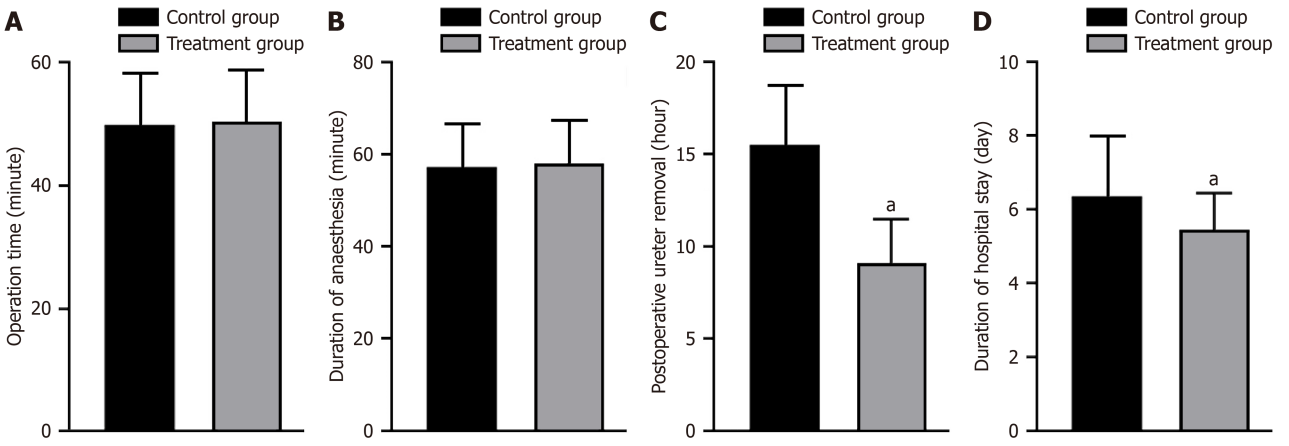

Figure 1 Comparison of perioperative indicators between the two groups of patients. A: Operation time; B: Duration of anaesthesia; C: Duration of postoperative ureter removal; D: Duration of hospital stay. $^aP < 0.05$ compared with control group.

levels, and immune function), descriptive statistics was used to present the data as means ± SD. Comparisons at different time points were analyzed using repeated-measures analysis of variance and *t*-tests. Categorical data (such as hernia location, place of residence, monthly family income, educational background, underlying diseases, and postoperative adverse reactions) were presented as rates and percentages (%). The χ^2 test was employed for comparison. The significance level was set at $\alpha = 0.05$. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, United States) or a similar statistical software package. Furthermore, this study identified outliers by calculating statistical indicators such as the mean and SD of the data. Specifically, when the value of a certain data point deviated from the mean by more than three times the SD, it was identified as an outlier. Given the relatively small sample size of this study, a method of retaining outliers was adopted for comprehensive analysis to ensure data quality and accuracy of the analysis results.

RESULTS

Comparison of basic patient characteristics between the two groups

No significant difference was found between the two groups in terms of age, site of inguinal hernia, place of residence, weight, monthly household income, educational status, and underlying diseases ($P > 0.05$; Table 1).

Comparison of perioperative indicators between the two groups

No significant difference was observed in the operative and anesthesia times between the two groups ($P > 0.05$). However, the treatment group had shorter postoperative urinary catheter removal time and hospital stay than the control group ($P < 0.05$; Figure 1).

Comparison of VAS scores at different time points between the two groups

No significant difference was found in preoperative VAS scores between the two groups ($P > 0.05$). However, at 12, 18, and 24 h after the surgery, the treatment group exhibited significantly lower VAS scores than the control group ($P < 0.05$; Figure 2).

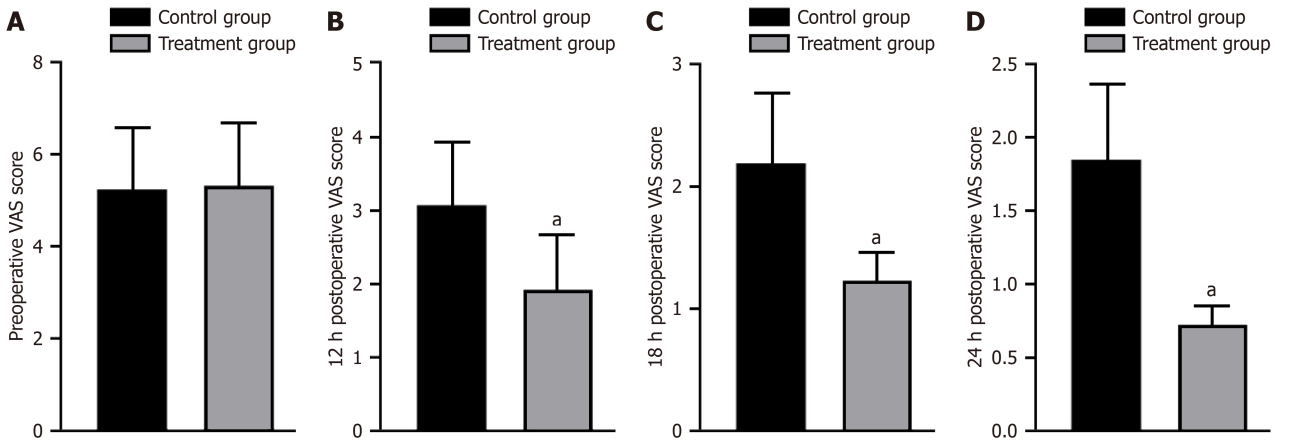

Figure 2 Comparison of perioperative visual analog scale scores between the two groups. A: Preoperative visual analog scale (VAS) score; B: 12 hours postoperative VAS score; C: 18 hours postoperative VAS score; D: 24 hours postoperative VAS score. $^{a}P < 0.05$ compared with control group. VAS: Visual analog scale.

Comparison of pre- and postoperative hemodynamic indexes between the two groups

The preoperative hemodynamic indexes were not significantly different between the two groups ($P > 0.05$). However, after the surgery, the HR increased, and the DBP and SBP decreased in both groups. Notably, the treatment group exhibited smaller changes in HR, DBP, and SBP than the control group ($P < 0.05$, Figure 3).

Comparison of pre- and postoperative stress levels between the two groups

No significant differences were found in the preoperative stress index levels between the two groups ($P > 0.05$). However, postoperative levels of cortisol, epinephrine, and norepinephrine significantly increased in both groups compared with their preoperative levels. In addition, the treatment group exhibited higher postoperative levels of cortisol, epinephrine, and norepinephrine than the control group ($P < 0.05$, Figure 4).

Comparison of preoperative and postoperative immune function between the two groups

No significant differences were observed in the comparison of preoperative immune function indicators between the two groups ($P > 0.05$). However, both groups exhibited higher postoperative levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ and lower levels of $CD8^+$ ($P < 0.05$). The treatment group exhibited higher levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ and lower levels of $CD8^+$ than the control group ($P < 0.05$; Figure 5).

Comparison of the incidence of postoperative adverse reactions between the two groups

The postoperative adverse reaction rates were 6.38% and 23.40% in the treatment and control groups, respectively, demonstrating a significant difference ($\chi^2 = 5.371$, $P = 0.020$). Notably, these reactions were well-tolerated and resolved spontaneously within 2 days (Table 2).

DISCUSSION

Groin hernia surgery is typically performed using conventional methods, which are associated with greater trauma and higher anesthesia requirements, potentially affecting patient recovery outcomes[11]. In contrast, laparoscopic groin hernia surgery offers advantages such as minimal invasiveness and higher safety, resulting in this wide adoption in the treatment of groin hernia. Although laparoscopic surgery reduces the anesthesia depth, a certain anesthesia level is still required owing to the need for artificial pneumoperitoneum during the procedure[12]. Inappropriate sedation can lead to excessive sympathetic nervous system response during anesthesia, resulting in increased intraoperative BP and HRF, thus delaying postoperative recovery and impeding rehabilitation[13]. Therefore, selecting the appropriate anesthesia approach to maintain stable hemodynamics and minimize effects on the patient is crucial for postoperative recovery.

General anesthesia is commonly used during laparoscopic surgery[14] because of its advantages such as rapid induction, optimal oxygenation and ventilation, and alleviation of patient anxiety and tension, thereby effectively minimizing adverse reactions. Total intravenous anesthesia (TIVA) is a widely adopted anesthetic technique in laparoscopic groin hernia surgery[15]. In TIVA, dexmedetomidine is commonly used as an anesthetic agent, which is a potent sedative with a rapid onset of action[16] and reaches peak concentration shortly after administration. Furthermore, dexmedetomidine exerts dose-dependent sedative and analgesic effects and allows for precise control of anesthesia by adjusting the dosage according to the patient's needs. Zhang *et al*[17] studied 102 patients aged > 65 years who had groin hernia and underwent open hernia repair surgery. They found that the addition of dexmedetomidine to ropivacaine enhanced postoperative analgesia during hospitalization, improved recovery quality, and did not affect chronic pain in older patients undergoing open hernia repair surgery. In this study involving middle-aged patients undergoing

Table 2 Comparison of the incidence of postoperative adverse reactions between the two groups, *n* (%)

Grouping	Number of examples	Dizziness	Nausea and vomiting	Dry mouth	Infection of the incision	Incidence
Control group	47	2 (4.26)	3 (6.68)	4 (7.55)	2 (4.26)	11 (23.40)
Treatment group	47	0 (0.00)	1 (2.13)	1 (2.13)	1 (2.13)	3 (6.38)
χ^2						5.371
P value						0.020

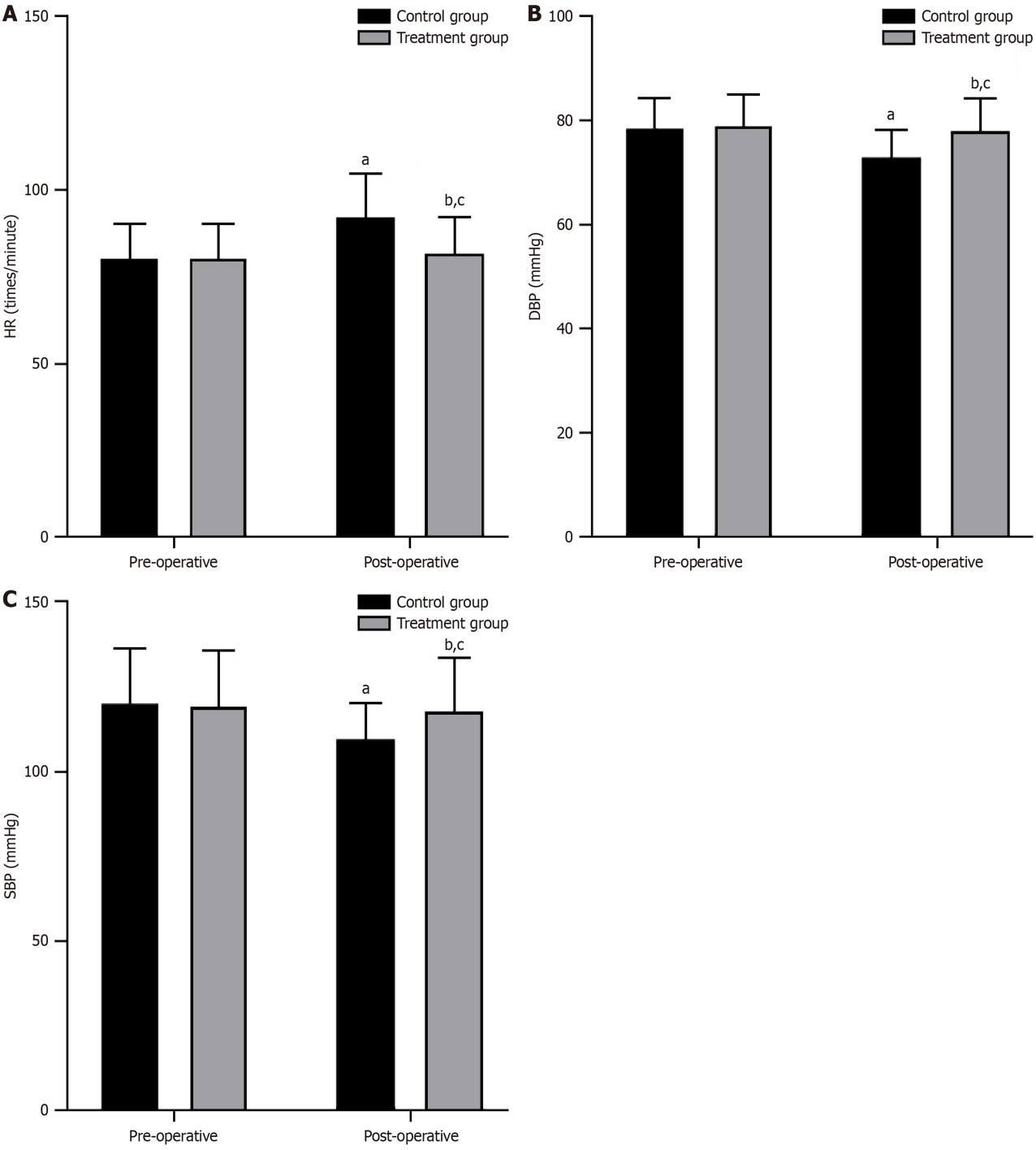

Figure 3 Comparison of pre- and post-operative haemodynamic parameters between the two groups. A: Heart rate levels; B: Diastolic blood pressure levels; C: Systolic blood pressure levels. [a]*P* < 0.05 compared with control group before treatment; [b]*P* > 0.05 compared with treatment group after treatment; [c]*P* < 0.05 compared with control group after treatment. HR: Heart rate; DBP: Diastolic blood pressure; SBP: Systolic blood pressure.

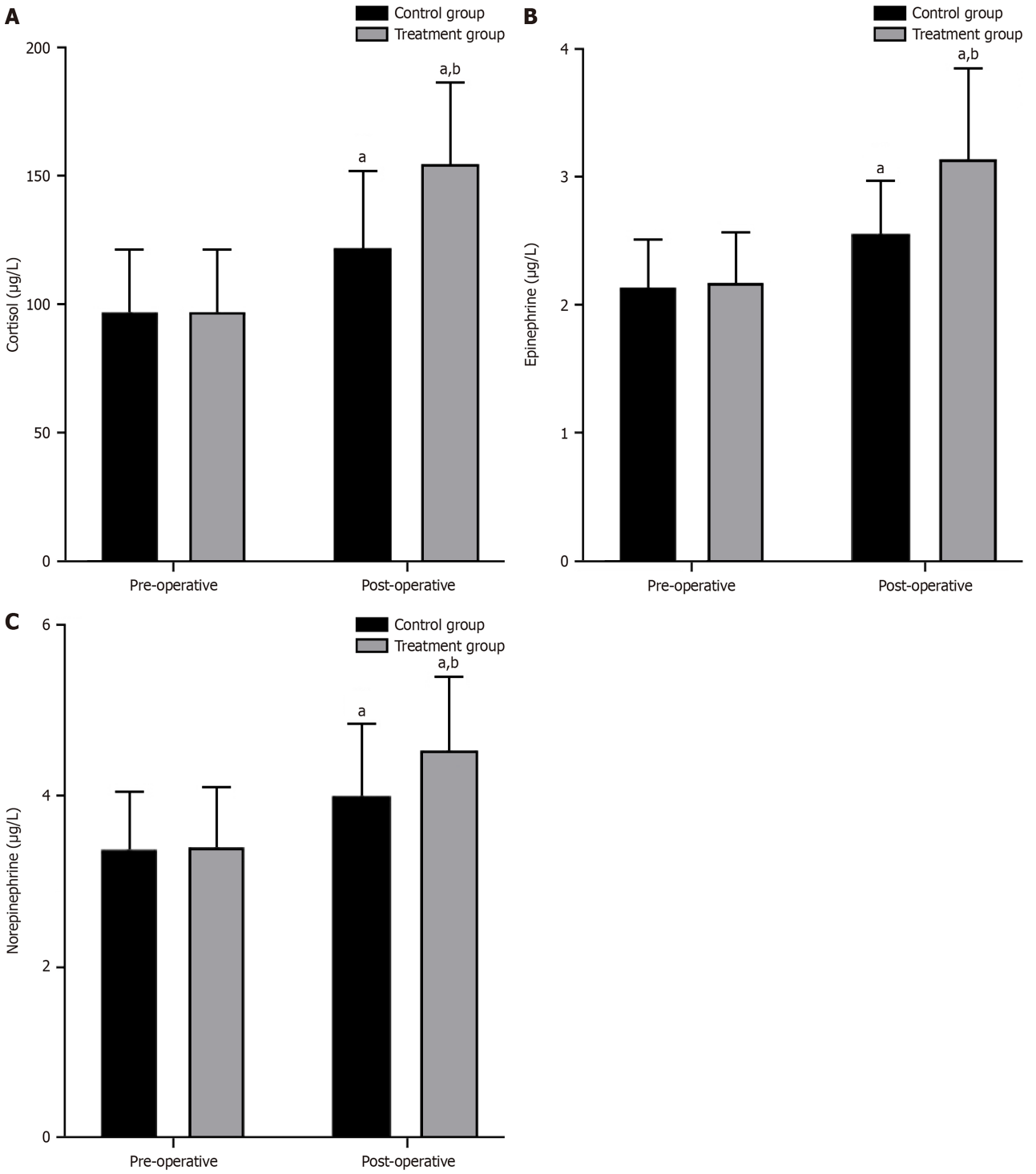

Figure 4 Comparison of pre- and post-operative stress levels between the two groups. A: Cortisol levels; B: Epinephrine levels; C: Norepinephrine levels. [a]*P* < 0.05 compared with preoperative; [b]*P* < 0.05 compared with control group postoperatively.

minimally invasive surgery, the treatment group had advantages regarding postoperative analgesic effects, time to removal of the urinary catheter, and length of hospital stay compared with the control group, indicating that dexmedetomidine-assisted intravenous-inhalation combined general anesthesia promotes early patient recovery. The treatment group had lower VAS scores than the control group at 12, 18, and 24 hours postoperatively, indicating significant analgesic effects of dexmedetomidine-assisted intravenous-inhalation combined general anesthesia. This may be attributed to the fact that dexmedetomidine acts as a selective α2-adrenergic receptor agonist possessing analgesic and sedative properties. It acts on the central nervous system to reduce pain transmission and elevate the pain threshold, thereby alleviating postoperative pain.

Stress indicators cortisol, epinephrine, and norepinephrine are important representative substances of the body's stress response[18]. Among them, cortisol is one of the main adrenal cortex hormones and has functions in anti-inflammatory response, immune suppression, and stress regulation. In laparoscopic minimally invasive surgery for groin hernia, both

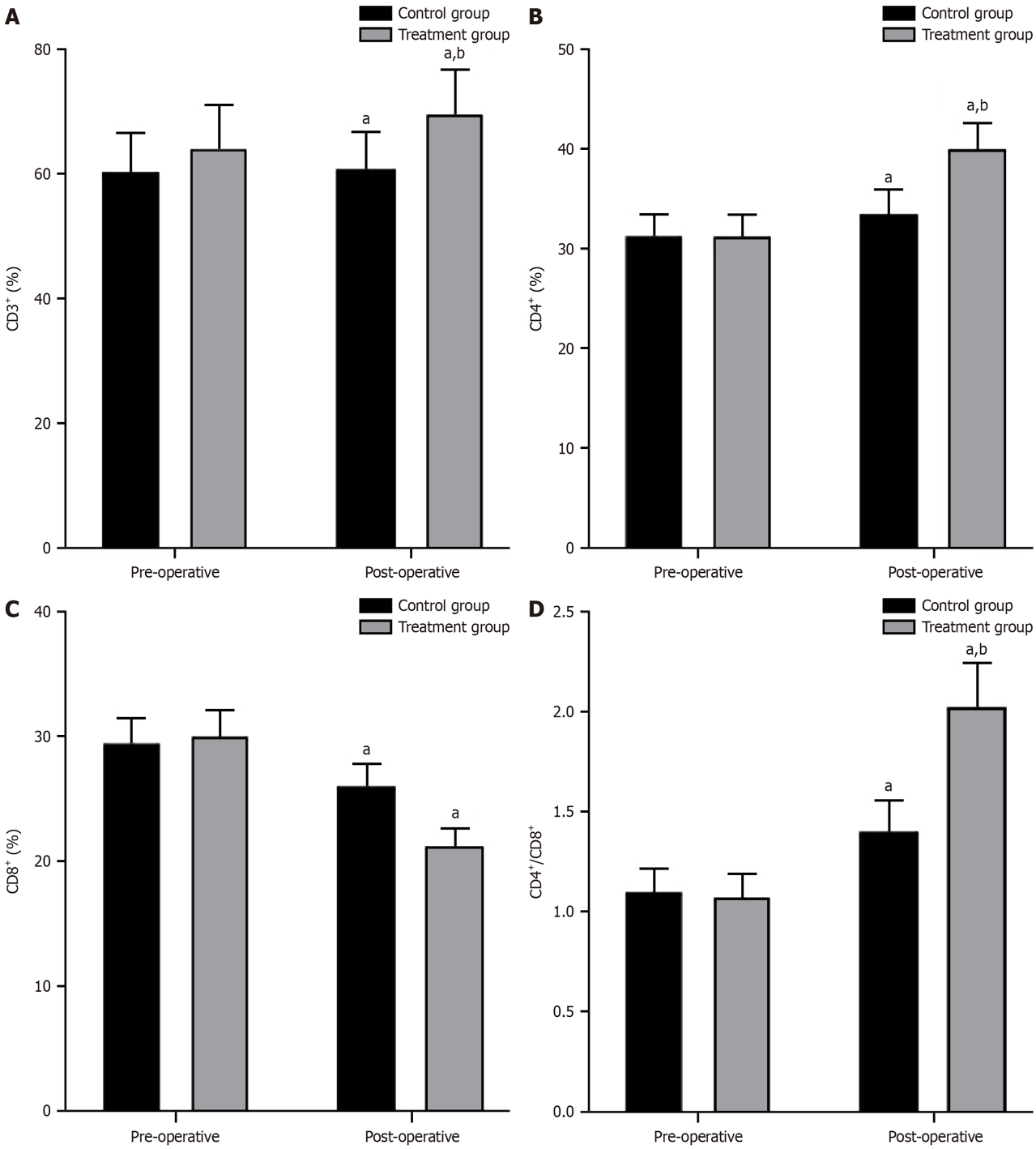

Figure 5 Comparison of immune function between the two groups before and after treatment. A: CD3+ levels; B: CD4+ levels; C: CD8+ levels; D: CD4+/CD8+ levels. [a]*P* < 0.05 compared with preoperative; [b]*P* < 0.05 compared with control group postoperatively.

surgical stimulation and the postoperative recovery process can elicit a stress response in the body, leading to high cortisol levels[19]. Monitoring cortisol levels can assess the stress severity intraoperatively and recovery status postoperatively[20]. Epinephrine and norepinephrine are secreted by the adrenal medulla and are primarily involved in the body's stress response, such as increased HR and high BP[21]. In laparoscopic minimally invasive surgery for groin hernia, surgical stimulation and the use of anesthetic drugs can induce the release of these hormones[22]. Monitoring these indicators can reflect the stress level during the surgery and the body's stress response[23]. The results regarding postoperative stress response and physiological indicators showed higher levels of cortisol, epinephrine, and norepinephrine in the treatment group than in the control group. The treatment group also exhibited smaller changes in HR, DBP, and SBP than the control group after the surgery. This finding indicates that dexmedetomidine-assisted intravenous-inhalation combined general anesthesia helps maintain the stability of blood flow in patients and reduces the effects of surgery on the circulatory system.

T lymphocytes are an important component of the body's immune regulation[24]. Among them, $CD3^+$ is used to evaluate the overall quantity and function of T lymphocytes[25]. $CD4^+$ is closely associated with cellular and humoral immunity and plays an important role in regulating and coordinating immune responses[26]. $CD8^+$ cells serve as markers for cytotoxic T lymphocytes and aid in killing infected or mutated cells[27]. The $CD4^+/CD8^+$ ratio serves as an indicator of immune balance, and changes in this ratio can be used to effectively evaluate immune function[28]. In this study, the postoperative levels of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$, and $CD8^+$ in the treatment group were higher than those in the control group, indicating that dexmedetomidine-assisted intravenous-inhalation combined general anesthesia can enhance overall immune function. Moreover, the incidence of postoperative adverse reactions in the treatment group (6.38%) was remarkably lower than that in the control group (23.40%). These findings highlight the enhanced postoperative safety associated with dexmedetomidine-assisted intravenous-inhalation combined general anesthesia and lower risk of adverse reactions. A potential explanation is that owing to its rapid onset of action, dexmedetomidine enables patients to rapidly achieve an anesthetic state within a short period, reaching peak concentration quickly after injection. It has a short duration of action because of fast metabolism and elimination, and patients recover quickly after discontinuing the medication, which helps reduce postoperative nausea, vomiting, and other adverse reactions.

However, this study has a few limitations. First, the sample size is relatively small, which may introduce certain selection bias. Second, the focus was only on laparoscopic minimally invasive surgery for groin hernia; thus, further research is needed for other types of minimally invasive surgeries.

CONCLUSION

Dexmedetomidine-assisted intravenous-inhalation combined general anesthesia promotes early recovery of patients after laparoscopic minimally invasive surgery for groin hernia. It ensures stable blood flow, enhances postoperative analgesic effect, reduces postoperative pain, alleviates stress response, improves immune function, facilitates anesthesia recovery, and provides greater safety.

FOOTNOTES

Author contributions: Lou QX and Xu KP contributed to conception, design, data analysis, and manuscript drafting and editing; Lou QX and Xu KP contributed to collection, assembly of data and revised the manuscript; Lou QX and Xu KP contributed to conception, resources, and manuscript review and editing; all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethic Committee of Yiwu Central Hospital.

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.

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ORIGINAL ARTICLE

Retrospective Study

Retrospective analysis on Lou Bei Er Chen decoction and acupuncture in gastroesophageal reflux disease post-gastric cancer surgery

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Abstract

BACKGROUND

Gastric cancer is a growing clinical challenge, particularly due to the increased risk of postoperative gastroesophageal reflux disease (GERD) following surgical treatment. traditional Chinese medicine (TCM), including acupuncture and herbal medicine, has been proposed as an adjunctive therapy to promote gastrointestinal recovery and alleviate GERD symptoms.

AIM

To retrospectively study the clinical efficacy of modified Lou Bei Er Chen decoction combined with acupuncture in treating patients with GERD after radical gastrectomy due to gastric cancer.

METHODS

A retrospective study was conducted, including patients with gastric cancer or malignant tumors of the stomach from January 2019 to December 2023 in the Affiliated Taizhou People's Hospital of Nanjing Medical University. Patients with a TCM diagnosis of qi depression and phlegm obstruction (n = 128) were selected on the basis of prescription and treatment principles. They were then divided into a control group (n = 61) and an observation group (n = 67). The control group received treatment with Western medicine domperidone. The observation group were treated with Lou Bei Er Chen decoction orally, with acupuncture at specific

acupoints (bilateral Hegu, bilateral Neiguan, and bilateral Zusanli), in addition to the treatment as in the control group, for a continuous treatment period of 8 weeks. The improvement time of postoperative gastrointestinal function indicators, gastrointestinal dysfunction scores, GERD-Q scores, and TCM syndrome scores were further observed for both groups.

RESULTS

The observation group showed significantly shorter times for first flatus, defecation, bowel sound recovery, and initiation of nasogastric enteral nutrition than the control group ($P < 0.05$). Upon treatment, the two groups demonstrated a significant reduction in gastrointestinal dysfunction scores, with a more significant reduction in the observation group ($P < 0.001$). The GERD-Q scores significantly decreased after 8 weeks of treatment in the two groups ($P < 0.05$), with a significant reduction in the observation group ($P < 0.05$), compared with baseline. The TCM syndrome scores significantly decreased after 4 and 8 weeks of treatment in the two groups ($P < 0.05$), with a significant reduction in the observation group ($P < 0.05$). The effective rate of the observation group after 8 weeks of treatment was significantly higher than that after 4 weeks ($\chi^2 = 13.648$, $P = 0.003$), and it was significantly higher than that of control group ($\chi^2 = 13.879$, $P = 0.003$).

CONCLUSION

Lou Bei Er Chen decoction combined with acupuncture treatment can effectively alleviate clinical symptoms in patients GERD after gastric cancer surgery and improve their life quality. It is worthy of further promotion and application.

Key Words: Lou Bei Er Chen decoction; Acupuncture; Gastric cancer; Gastroesophageal reflux disease; Gastrointestinal function

Core Tip: This study evaluates the effectiveness of combining acupuncture with Lou Bei Er Chen decoction in improving postoperative gastrointestinal recovery and reducing gastroesophageal reflux disease symptoms in patients with gastric cancer. This integrated approach significantly shortens the time to first flatus, defecation, and bowel sound recovery, while also reducing traditional Chinese medicine (TCM) syndrome scores and gastroesophageal reflux disease-Q scores. The improvements in TCM syndrome scores were observed at 4 weeks post-treatment. This study provides evidence for the potential of TCM as an adjunctive therapy to enhance postoperative recovery and quality of life in patients with gastric cancer.

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INTRODUCTION

Gastric cancer is currently recognized as one of the top five cancers globally, ranking third in terms of mortality. The number of deaths due to gastric cancer accounts for 8.8% of deaths related to cancer annually[1,2]. Therefore, early screening, detection, and treatment are crucial for improving survival rates in patients with gastric cancer. Presently, surgical tumor resection remains the primary and most effective treatment for gastric cancer[3]. However, radical gastrectomy alters the structure of the digestive tract, leading to abnormal absorption function and various complications. Gastroesophageal reflux disease (GERD) is a serious post-gastric cancer surgery complication. For most patients, the use of proton pump inhibitors, H2 receptor antagonists, prokinetic agents, and other medications has yielded unsatisfactory results[4].

Modern medicine currently lacks pharmaceutical interventions to improve and repair GERD esophageal motility. Traditional medicine has been inherited and developed through innovation, and traditional Chinese medication has demonstrated certain advantages in treating GERD, showing some efficacy in improving esophageal motility. GERD falls into the categories of "acid regurgitation", "chest stuffiness", and "esophageal obstruction" in traditional Chinese medicine (TCM). The key pathogenesis lies in the spleen's failure to control the descending of stomach qi, thus leading to the upward rebellion of stomach qi, often caused by spleen and stomach deficiency, liver qi stagnation, phlegm turbidity, and dysfunction in ascending and descending qi regulation[5].

Acupuncture, as an integral part of TCM with a history spanning several thousand years, is widely applied in the treatment of various diseases, including gastrointestinal disorders such as GERD[6]. According to TCM theory, acupuncture regulates the flow of qi within the body by stimulating specific acupoints, thereby restoring the body's

balance[7]. In TCM, GERD is often categorized under the pattern of qi stagnation and phlegm obstruction, characterized by upward rebellion of stomach qi, which is closely related to factors such as spleen deficiency, liver depression, and phlegm turbidity[8]. Acupuncture alleviates these symptoms by promoting the smooth flow of qi through the meridians and harmonizing the functions of the internal organs. Modern research has shown that acupuncture can activate the parasympathetic nervous system, enhancing gastrointestinal motility, reducing inflammatory responses, and releasing neurotransmitters such as serotonin and endorphins, which can alleviate pain and improve overall health status[9]. Additionally, acupuncture can influence gastric acid secretion and the function of the lower esophageal sphincter, both of which play crucial roles in the pathogenesis of GERD[10]. Clinically, acupuncture has been proven to be effective in treating GERD, with multiple randomized controlled trials demonstrating that it can significantly relieve symptoms such as heartburn, reflux, and dyspepsia, reduce the frequency and severity of symptoms, improve quality of life, and decrease dependence on medications[11,12]. Moreover, previous studies have indicated that Lou Bei Er Chen decoction has therapeutic effects on GERD post-gastric cancer surgery[13]. Due to the complexity of the disease, the combination of acupuncture and herbal medicine treatment often enhances therapeutic efficacy. Therefore, this study retrospectively analyzed the clinical efficacy of using Lou Bei Er Chen decoction in conjunction with acupuncture for the treatment of GERD post-gastric cancer surgery in our hospital over the past 5 years.

MATERIALS AND METHODS

Subject selection

Data of patients who were admitted to the Affiliated Taizhou People's Hospital of Nanjing Medical University from January 2019 to December 2023 and initially diagnosed with gastric cancer or gastric malignant tumors were screened through the hospital information system. A retrospective study was conducted on their case data. All patients had a confirmed pathological diagnosis to avoid situations where the initial diagnosis by the attending physician may lead to incongruities between diagnosis and treatment. Patients were selected on the basis of their prescription medication and treatment principles to identify those with a TCM diagnosis of qi stagnation and phlegm obstruction syndrome in gastric cancer. This study was approved by the Ethics Committee of the Affiliated Taizhou People's Hospital of Nanjing Medical University.

Diagnostic criteria

Diagnostic criteria in western medicine: Gastric cancer diagnosis was confirmed in accordance with Clinical Diagnosis and Treatment Guidelines for Gastric Cancer (2021 Edition)[14], and strict adherence to the indications for surgical treatment for gastric cancer was followed. Diagnosis criteria were established in accordance with the Evidence-based Clinical Practice Guidelines for the GERD (2021) and the 2020 Chinese Expert Consensus on GERD[15,16]. Symptoms included epigastric burning sensation, heartburn, reflux, belching, and chest discomfort (excluding cardiac factors), and the result confirmed by endoscopy and proton pump inhibitor trial.

Diagnostic criteria in TCM: The diagnostic criteria were formulated in accordance with the 2020 Chinese Expert Consensus on the GERD[16]. Principal symptoms of qi stagnation and phlegm obstruction syndrome included: (1) Discomfort in the throat, aggravated by emotional stress; (2) Chest discomfort; and (3) Heartburn and acid reflux. Secondary symptoms of qi stagnation and phlegm obstruction syndrome included: (1) Belching or reflux; (2) Hoarse voice; (3) Epigastric distention; and (4) Mental depression. Examination of tongue and pulse included: Pale red tongue with a greasy or thick white coating and wiry and slippery pulse. Syndrome confirmation included: Presence of two principal symptoms and one or two secondary symptoms, in conjunction with tongue and pulse examination.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Preoperative gastroscopy and diagnosis of gastric cancer with pathological results; (2) TCM diagnosis of qi stagnation and phlegm obstruction syndrome; (3) Meeting the indications for radical gastrectomy for gastric cancer; (4) Scheduled for laparoscopically assisted radical gastrectomy for gastric cancer; (5) Aged 18-75 years, any gender; and (6) Good compliance, ability to understand, and informed consent signed.

The exclusion criteria were as follows: (1) Advanced gastric cancer, distant metastasis; (2) Conversion to open surgery during operation; (3) Presence of surgical contraindications; (4) History of diabetes, infection, fever, or other diseases affecting systemic inflammatory stress before surgery; (5) History of immune or neuroendocrine system diseases; (6) Prior use of drugs affecting the immune or neuroendocrine system before surgery; (7) Presence of skin damage or infection at the acupuncture points; (8) Severe cardiovascular or cerebrovascular complications, active hepatitis, or abnormal liver and kidney function; (9) Severe cognitive impairment; and (10) Pregnancy and lactation.

Treatment methods

Patients receiving conventional Western medical treatment were categorized as the control group, totaling 61 cases, whereas those receiving acupuncture and herbal medicine treatment in addition to the conventional Western medical treatment were categorized as the observation group, totaling 67 cases.

Primary treatment: In accordance with the Standardized Diagnosis and Treatment Guidelines for Gastric Cancer (Trial), standard laparoscopic radical gastrectomy was performed, with intraoperative placement of a nasogastric-jejunal feeding

tube, and the surgery was completed by the same physician and surgical team. Postoperatively, routine perioperative treatment measures were taken, including fasting, routine radiotherapy and chemotherapy, gastrointestinal decompression, intravenous fluid replacement, nutritional support, and infection prevention. After the patients' vital signs stabilized 6 hours postoperatively, they were encouraged to assume a semi-recumbent position, and, with the drainage tube protected, they were encouraged to turn over on their own.

Control group: The patients were given domperidone capsules (manufactured by Xi'an Janssen Pharmaceutical Ltd., batch number: National Drug Approval H10910003, specification: 10 mg × 30 tablets for oral administration) at 10 mg dose three times during daytime before meals, continuously for a total of 8 weeks.

Treatment group (addition of Lou Bei Er Chen decoction and acupuncture to the control group): Oral administration of Lou Bei Er Chen decoction included: The herbal formula consists of 30 g of Gualou (*Trichosanthes Kirilowii*), 15 g of Zhebeimu (*Thunberg Fritillary Bulb*), 10 g of Fabanxia (*Pinellia Ternata*), 15 g of Chenpi (*Tangerine Peel*), 10 g of Fuling (*Poria*), 30 g of Haipiaoxiao (*Sepia*), 30 g of Walengzi (*Ark Shell*), 15 g of Xuanfuhua (*Inula Britannica*), 15 g of Zheshi (*Hematite*), 30 g of Weilingxian (*Clematis Chinensis*), 20 g of Zhishi (*Aurantii Fructus*), 15 g of Laifuzi (*Raphani Semen*), and 10 g of Gancao (*licorice*). For patients with remarkable pain in the flanks, severe acid reflux, and severe vomiting, 6 g of Huanglian (*Coptidis Rhizoma*), 6 g of Wuzhuyu (*Evodiae Fructus*), and 20 g of Yanhusuo (*corydalis*) are added; for those with significant fatigue, 30 g of Huangqi (*Astragali Radix*) and 20 g of Taizishen (*Pseudostellariae Radix*) were added; for those with poor appetite and anorexia, 15 g of Jingshanzha (*Crataegi Fructus*), 15 g of Maiya (*Hordei Fructus Germinatus*), and 15 g of Jineijin (*Ventriculi Galli Mucosa*) were added; for those with depression and emotional instability, 30 g of Hehuanpi (*Albiziae Cortex*), 15 g of Yujin (*Curcumae Radix*), and 10 g of Baihe (*Lilii Bulbus*) were added. The decoction was prepared by boiling in water, taken two times daily, 100 mL each time, 30 min to 1 h after breakfast and dinner, for 8 weeks. Acupuncture treatment included the following acupoints: Bilateral Hegu, bilateral Neiguan, bilateral Zusanli, and other points. The positioning was in accordance with the Standardized Nomenclature and Location of Acupoints (GB/T12346-2006). The acupuncture time was three times a week (every other day, with 2 days of rest after every three times), leaving the needles in for about 30 minutes each time, for 8 weeks of continuous treatment.

Indicator monitoring

Baseline characteristics: The baseline characteristics of the patients included gender, age, body mass index, surgical method, course of disease, pathological staging, and surgical approach.

Efficacy indicators: (1) Time for improvement of postoperative gastrointestinal function: The specific time of anal gas and stool passage, restoration of bowel sounds, and initiation of nasogastric-jejunal feeding tube feeding was recorded starting 6 hours postoperatively, with checks every 2 hours; (2) Gastrointestinal Function Disturbance score: In accordance with the Expert Consensus on Prevention and the Treatment of Postoperative Gastrointestinal Dysfunction [17], the severity of postoperative gastrointestinal dysfunction was graded on a 4-point scale, including scores of 0, 1, 2, and 3 for eating, nausea, vomiting, physical examination, and duration of symptoms, with a total score range of 0-15; (3) GERD-Q Scale score: This scale was scored separately for positive and negative symptoms, with a score of 8 indicating support for a GERD diagnosis, with a maximum score of 18. This questionnaire scale can serve as a diagnostic tool and provide an overall assessment of quality of life and clinical efficacy of patients with GERD[18]. The scores were assessed before treatment, 4 weeks after treatment, 8 weeks after treatment; and (4) Score of TCM syndrome: This score was formulated in accordance with the Chinese Expert Consensus on GERD (2020)[16], with changes in symptom quantification grading scores used to assess efficacy. The patients were considered cured if the symptoms and signs disappeared or were basically eliminated, with index for efficacy ≥ 95%. Significant improvement indicated that symptoms and signs greatly improved, with 70% ≤ efficacy index < 95%. Effectiveness was shown if the clinical symptoms and signs showed improvement, with 30% ≤ efficacy index < 69%. Ineffectiveness indicated that no improvement in clinical symptoms and signs was observed, with efficacy index < 30%. The total effective rate was calculated as follows: Total effective rate (%) = (number of cured cases + number of significantly improved cases + number of effective cases)/total number of cases × 100%. The scores were assessed before treatment, 4 weeks after treatment, and 8 weeks after treatment.

Statistical analysis

SPSS (version 26.0) software was applied for statistical analysis. Count data were generally described by rate, and χ^2-tests was used. Normally distributed measurement data were demonstrated as (mean ± SD), and if data were normally distributed and had homogeneity of variance, *t*-test or analysis of variance was used. Repeated measurement data were analyzed using repeated measures analysis of variance. Non-normally distributed data were analyzed *via* rank sum test. *P* value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

From January 2019 to December 2023, 128 patients diagnosed as gastric cancer in the hospital and meeting the inclusion and exclusion criteria were enrolled. Among them, 67 were in the observation group, and 61 were in the control group. No significant differences were found in the general clinical data, such as age gender, body mass index, disease course,

tumor staging, and surgical methods, between groups ($P > 0.05$). The clinical data were comparable between groups (Table 1).

Improvement in postoperative gastrointestinal function indicators

The time for the first flatus, defecation, restoration of bowel sounds, and initiation of enteral nutrition *via* nasogastric-jejunal tube after surgery in the observation group was significantly shorter than that in the control group ($P < 0.05$) (Table 2).

Comparison of gastrointestinal dysfunction scores between groups

Before treatment, no significant differences were observed in gastrointestinal dysfunction scores between groups. The gastrointestinal dysfunction scores in both groups decreased significantly after treatment, with a more significant reduction observed in the observation group ($P < 0.001$) (Table 3).

Comparison of GERD-Q scores between groups

Before treatment, no significant differences were observed in GERD-Q scores between groups. After treatment, the GERD-Q scores at 8 weeks significantly decreased compared with those before treatment ($P < 0.05$). Compared with the control group, the observation group showed significantly decreased GERD-Q scores at 8 weeks after treatment ($P < 0.05$) (Figure 1A).

Comparison of TCM syndrome scores

Before treatment, no significant differences were observed in TCM syndrome scores between groups. After treatment, the TCM syndrome scores at 4 and 8 weeks showed a significant decrease compared with those before treatment ($P < 0.05$). Compared with the control group, the observation group demonstrated significantly decreased TCM syndrome scores at 4 and 8 weeks after treatment ($P < 0.05$) (Figure 1B).

Comparison of efficacy of TCM syndrome

The effective rate of the observation group at 8 weeks treatment was significantly higher than the effective rate at 4 weeks ($\chi^2 = 13.648$, $P = 0.003$), with no statistically significant difference in the control group ($\chi^2 = 4.428$, $P = 0.219$). No statistically significant difference was observed in the effective rate between groups at 4 weeks of treatment ($\chi^2 = 7.334$, $P = 0.062$). Meanwhile, the effective rate of the observation group was significantly higher than the effective rate of the control group at 8 weeks of treatment ($\chi^2 = 13.879$, $P = 0.003$) (Table 4).

DISCUSSION

As the only possible method for patients with gastric cancer to achieve a cure, surgery can effectively remove tumor cells and tissues, aiming to prolong survival period and improve the life quality of patients. Postoperative GERD may occur in some patients; it is one of the major complications affecting life quality and significantly increasing the risk of adverse outcomes[19]. Therefore, timely relief of clinical symptoms of GERD is crucial for treatment[20]. Western medicine approaches the treatment of GERD mainly with prokinetic agents and acid-suppressing drugs. Mild patients can temporarily alleviate symptoms with acid-suppressing drugs[21]. However, GERD tends to recur, and some patients quickly relapse after discontinuation of medication[22], often requiring long-term drug use, inadvertently increasing the economic burden on patients and prolonging the treatment duration. According to the TCM records of clinical symptoms, such as acid regurgitation and heartburn, the disease categories of "acid regurgitation," "esophageal obstruction", "noisy throat", and "globus hystericus" can generally summarize the characteristics of GERD syndrome[23]. The main pathogenesis is the upward reversal of stomach qi, related to liver depression and stagnation, stomach dysfunction, and abnormal distribution of body fluids. The patients in this study were diagnosed with qi depression and phlegm obstruction syndrome, manifested as stuffiness in the epigastrium, vomiting, and swallowing difficulties. Treatment should focus on resolving phlegm, regulating qi, and relaxing the chest. The observation group was treated with Lou Bei Er Chen decoction. A combination of Loubei powder and Erchen decoction, Lou Bei Er Chen decoction is flexibly used on the basis of patients' symptoms, playing a role in dispersing chest congestion, regulating qi, resolving phlegm, and clearing and opening the throat.

The Gualou in the prescription regulates qi and disperses chest congestion[24], and when used with Zhebeimu, it has the effect of clearing heat and transforming phlegm. Ginger and Banxia resolve phlegm and descend qi. Fuling and Houpo strengthen the spleen and eliminate dampness. Zhuru and Huangqin clear heat and transform phlegm. Zhishi, Xuanfuhua, and Daizheshi regulate qi and descend rebellious qi, and Gancao harmonizes the other herbs[25]. By using a large dose of chest-dispersing and phlegm-resolving herbs, combined with a large amount of phlegm-resolving herbs and strengthening the spleen to treat the source of phlegm, the prescription achieves the effects of dispersing chest congestion, regulating qi, and transforming phlegm. Additionally, the treatment effectiveness can be enhanced by combining clinical symptoms with adjustments, thus strengthening the clinical efficacy.

Gastric cancer surgery damages the function of the spleen and stomach, consumes qi, and injures blood, leading to damage to the abdominal meridians, stasis of the channels, and stagnation of qi[26]. Therefore, treatment should focus on regulating functions of the spleen and stomach, descending stomach qi, and smoothing qi circulation. Acupoints near the abdominal incision should be avoided, with most selections being from the limbs, with Zusanli being the most commonly chosen. In this study, acupoints from the Jueyin and Yangming meridians were selected, including Hegu, Neiguan, and

Table 1 Comparison of clinical data of patients, *n*

	Observation (*n* = 67)	Control (*n* = 61)	χ^2/*t*/*Z*	*P* value
Age, years	44.35 ± 14.25	48.77 ± 11.96	1.89	0.06
Male, *n* (%)	47 (70.15)	46 (75.41)	0.44	0.50
BMI, kg/m^2	22.46 ± 2.72	22.00 ± 2.28	1.03	0.30
Disease course, months	21.98 ± 8.00	19.40 ± 8.04	1.82	0.07
Tumor staging			2.30	0.51
I	13	11		
II	25	20		
III	23	19		
IV	6	11		
Surgical methods			0.05	0.98
Proximal gastrectomy	2	2		
Total gastrectomy	22	19		
Distal gastrectomy	43	40		

BMI: Body mass index.

Table 2 Comparison of postoperative improvement of gastrointestinal function indicators between groups, hours

	Flatus	Defecation	Restoration of bowel sounds	Enteral nutrition *via* nasogastric-jejunal tube
Control (*n* = 61)	76.32 ± 9.11	96.21 ± 11.21	52.30 ± 6.45	78.25 ± 8.26
Observation (*n* = 67)	71.21 ± 8.32	81.88 ± 9.20	31.03 ± 4.25	71.55 ± 8.23
t	3.30	7.86	21.80	4.59
P value	0.001	< 0.001	< 0.001	< 0.001

Zusanli[27]. Hegu is the original point of Hand-Yangming large intestine meridian[28]. As it intersects with Foot-Yangming stomach meridian, the two seek the same qi[29]. Thus, Hegu can regulate the qi of the stomach and intestines and has a significant therapeutic effect on gastrointestinal diseases[30]. Neiguan is the Luo point of Hand-Jueyin pericardium meridian, which does not belong to Sanjiao meridian. Sanjiao primarily governs digestion, transportation of qi, and fluid circulation, so Neiguan has the function of descending stomach qi, regulating qi, and connecting the channels[31]. Neiguan is also connected to the Yinwei meridian, which enters the abdomen, and thus can regulate abdominal diseases. As a characteristic therapy of TCM, acupuncture stimulates local acupoints to regulate qi circulation and harmonize qi and blood[32]. Therefore, acupuncture can balance Yin and Yang while harmonizing qi and blood.

During perioperative comprehensive treatment process of gastric cancer, the recovery of gastrointestinal function after surgery is a critical stage and a major indicator of overall postoperative recovery[33,34]. The results of the current study showed that the time for first flatus, bowel movement, restoration of bowel sounds, and initiation of enteral nutrition *via* a nasogastric-jejunal tube in the observation group was significantly shorter than that in the control group. The gastrointestinal dysfunction scores were reduced, indicating that the combination of acupuncture and herbal medicine can significantly promote postoperative gastrointestinal function and facilitate enhanced recovery. The results showed that the TCM syndrome scores in both groups decreased after treatment, but the decrease in the observation group was more pronounced than that in the control group, indicating improvement of TCM syndromes by Lou Bei Er Chen decoction and acupuncture, similar to the results from Xu *et al*[35]. GERD-Q[36] scores are a sensitive, noninvasive, diagnostic screening tool used for GERD diagnosis in general patients. After treatment, the TCM syndrome scores and GERD-Q scores decreased, with a more significant reduction in the observation group than in the control group. Furthermore, the clinical effective rate in the observation group was significantly higher than that in the control group, indicating that the combined treatment of acupuncture and herbal medicine for GERD mutually promotes each other, yielding significantly enhanced clinical efficacy. This study unveiled the advantages of TCM or integrated traditional and Western medicine in treating GERD from multiple dimensions and pathways[37].

The current study involved 128 patients with gastric cancer who underwent surgery, which is a relatively moderate sample size for a pilot study. While this number is sufficient to demonstrate the preliminary effectiveness of the combined treatment of acupuncture and herbal medicine in promoting postoperative gastrointestinal recovery and alleviating GERD symptoms, it may not be universally applicable to all populations. Several factors should be considered

Table 3 Comparison of gastrointestinal dysfunction scores between groups

	Before treatment	After treatment	*t*	*P* value
Control (*n* = 61)	7.48 ± 0.91	3.12 ± 0.42	33.976	< 0.001
Observation (*n* = 67)	7.49 ± 0.84	1.98 ± 0.36	49.351	< 0.001
t	0.064	16.529		
P value	0.949	< 0.001		

Table 4 Comparison of efficacy of traditional Chinese medicine syndrome between groups, *n*

	Time, weeks	Cured	Significant improvement	Effective	Ineffective	Effective rate, %
Observation (*n* = 67)	4 weeks	1	8	40	18	73.13
	8 weeks	5	23	27	12	82.09
Control (*n* = 61)	4 weeks	0	3	29	29	52.46
	8 weeks	2	6	32	21	65.57

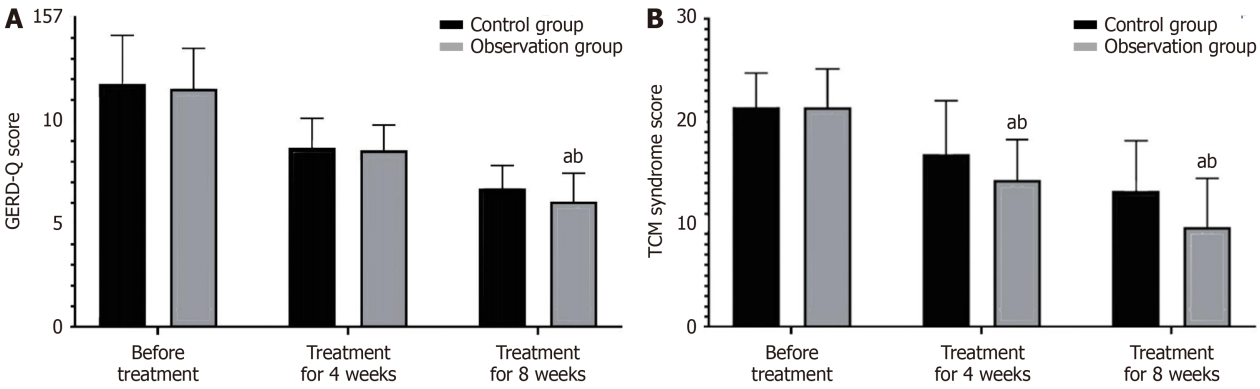

Figure 1 Comparison of gastroesophageal reflux disease-Q scores and traditional Chinese medicine syndrome scores. A: Gastroesophageal reflux disease-Q scores; B: Traditional Chinese medicine syndrome scores. Compared with scores before treatment, [a]*P* < 0.05; compared with control group after treatment, [b]*P* < 0.05. GERD: Gastroesophageal reflux disease; TCM: Traditional Chinese medicine.

when interpreting the generalizability of our findings. First, the study was conducted in a single center, and the participants were primarily from a specific geographic region, which may limit the external validity of the results. Different populations, particularly those with varying genetic backgrounds, dietary habits, and cultural practices, may respond differently to the same treatment regimen. For example, the effectiveness of acupuncture and herbal medicine may vary depending on the prevalence of certain comorbidities or the availability of traditional medical resources in different regions. Second, while the study demonstrated significant improvements in gastrointestinal function and GERD symptoms, the long-term effects of the combined treatment remain unclear. While the current study provides promising evidence for the use of acupuncture and herbal medicine in managing postoperative GERD in patients with gastric cancer, the results should be interpreted with caution. Further research is necessary to validate these findings in larger, more diverse populations and to explore the long-term outcomes of this treatment approach.

CONCLUSION

In summary, the combination of Lou Bei Er Chen decoction and acupuncture for the treatment of postoperative GERD in patients with gastric cancer can help rapidly restore gastrointestinal function, alleviate clinical symptoms, reduce patient suffering, and improve quality of life. It is relatively safe with no significant adverse events and worthy of further clinical promotion and application.

FOOTNOTES

Author contributions: Shi JH and Jiang S designed the experiments and conducted clinical data collection, wrote the original manuscript, and revised the paper; Yang H, Wang ST, Wang WJ, Shi Y, and Huang SS performed postoperative follow-up and recorded the data, conducted the collation and statistical analysis; and all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Imaging features and correlation with short-term prognosis in laparoscopic radical resection of colorectal cancer

Ze-Hui Fang, Ai-Hua Hao, Yuan-Gang Qi

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a malignant tumor with high morbidity and mortality rates worldwide. With the development of medical imaging technology, imaging features are playing an increasingly important role in the prognostic evaluation of CRC. Laparoscopic radical resection is a common surgical approach for treating CRC. However, research on the link between preoperative imaging and short-term prognosis in this context is limited. We hypothesized that specific preoperative imaging features can predict the short-term prognosis in patients undergoing laparoscopic CRC resection.

AIM

To investigate the imaging features of CRC and analyze their correlation with the short-term prognosis of laparoscopic radical resection.

METHODS

This retrospective study conducted at the Affiliated Cancer Hospital of Shandong First Medical University included 122 patients diagnosed with CRC who underwent laparoscopic radical resection between January 2021 and February 2024. All patients underwent magnetic resonance imaging (MRI) and were diagnosed with CRC through pathological examination. MRI data and prognostic indicators were collected 30 days post-surgery. Logistic regression analysis identified imaging features linked to short-term prognosis, and a receiver operating characteristic (ROC) curve was used to evaluate the predictive value.

RESULTS

Among 122 patients, 22 had irregular, low-intensity tumors with adjacent high signals. In 55, tumors were surrounded by alternating signals in the muscle layer.

In 32, tumors extended through the muscular layer and blurred boundaries with perienteric adipose tissue. Tumor signals appeared in the adjacent tissues in 13 patients with blurred gaps. Logistic regression revealed differences in longitudinal tumor length, axial tumor length, volume transfer constant, plasma volume fraction, and apparent diffusion coefficient among patients with varying prognostic results. ROC analysis indicated that the areas under the curve for these parameters were 0.648, 0.927, 0.821, 0.809, and 0.831, respectively. Sensitivity values were 0.643, 0.893, 0.607, 0.714, and 0.714, and specificity 0.702, 0.904, 0.883, 0.968, and 0.894 ($P < 0.05$).

CONCLUSION
The imaging features of CRC correlate with the short-term prognosis following laparoscopic radical resection. These findings provide valuable insights for clinical decision-making.

Key Words: Colorectal cancer; Imaging features; Laparoscopic radical resection; Short-term prognosis; Tumor signal; Prognostic indicators

Core Tip: Colorectal cancer (CRC) is recognized as a highly prevalent and deadly malignant tumor that affects many patients globally. This study analyzed preoperative magnetic resonance imaging (MRI) data and 30-day postoperative prognostic indicators by using logistic regression and receiver operating characteristic curves. The key findings highlight the role of MRI in predicting short-term outcomes after laparoscopic radical resection, emphasizing the importance of imaging-derived indicators. These insights enhance the prognostic accuracy and guide tailored treatment approaches for patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC), a prevalent malignant tumor of the digestive system, often initially manifests as subtle changes in bowel habits, diarrhea, and hematochezia. As the condition progresses, patients may exhibit systemic symptoms, including weight loss and anemia. Poor lifestyle, genetic predisposition, and intestinal inflammation contribute to its development[1,2]. With recent developments and the popularization of laparoscopic technology, laparoscopic radical resection has become a common surgical method for treatment[3,4]. However, the prognoses of these patients vary significantly. Therefore, it is important to identify a reliable method to predict the short-term prognosis of patients. Magnetic resonance imaging (MRI) has a high resolution and lesion detection rate. Through MRI examination, the relationship between the tumor and colorectal wall can be accurately displayed, as well as the speed and process of contrast agent clearance from the lesion. This capability allows for direct assessment of the microcirculation of the lesion, which is highly valuable in the prognostic evaluation of CRC[5]. This study analyzed the imaging features of CRC and explored their correlation with the short-term prognosis of laparoscopic radical resection to provide a basis for clinical decision-making.

MATERIALS AND METHODS

Patient characteristics

Between January 2021 and February 2024, 122 patients diagnosed with CRC who underwent radical laparoscopic surgery at the Affiliated Cancer Hospital of Shandong First Medical University were included in this study. Postoperative imaging data, before surgery, and prognostic indicators 30 days after surgery were systematically collected. Based on their postoperative outcomes, patients were categorized into a favorable prognosis group ($n = 94$) and a poor prognosis group ($n = 28$). The favorable prognosis group comprised 55 males and 39 females, with ages ranging from 34 to 77 years and an average age of 57.60 ± 8.56 years. The poor prognosis group included 18 males and 10 females, aged between 45 and 71 years, with an average age of 57.61 ± 8.04 years. All patients presented with varying degrees of symptoms, such as hematochezia, abdominal discomfort, dyspepsia, and abnormal bowel movements. The distribution of tumor types was as follows: 38 cases of rectal cancer, 36 cases of sigmoid colon cancer, 20 cases of transverse colon cancer, 15 cases of rectosigmoid junction cancer, nine cases of descending colon cancer, and four cases of ileocecal cancer.

Eligibility for the study was determined using the following criteria: First, participants had not undergone radiotherapy, chemotherapy, or any other form of treatment before surgical intervention. Second, the inclusion criteria were limited to those patients who had received a pathological diagnosis of CRC. Third, all the patients in this study underwent laparoscopic radical resection at our facility. Finally, only those individuals with complete and available medical

records were included. Exclusion from the study was based on specific conditions: Individuals who were currently lactating or pregnant were excluded. Additionally, patients with documented abnormalities in vital organ function, such as the heart, liver, or kidneys, were excluded from the study. The study was reviewed and approved by the Institutional Review Board of the Affiliated Cancer Hospital of Shandong First Medical University (Approval No.2024007003).

MRI examination

A 1.5T MRI system equipped with an 8-channel phased-array body coil was used in this study. The participants were placed in the supine position with their feet forward during the procedure. Initial tumor localization was performed, followed by sequential imaging in both the cross-sectional and coronal planes with the tumor as the focal point. The technical parameters for the scans were as follows: 5 mm slice thickness with a corresponding 5 mm gap. For T1-weighted imaging, the parameters included a repetition time (TR) of 620 millisecond and an echo time (TE) of 6 millisecond within a scanning field of view (FOV) of 32 cm × 32 cm. Axial T2-weighted imaging (T2WI) without fat suppression featured a TR of 2600 millisecond and (TE) of 80 millisecond, with a FOV of 32 cm × 32 cm. Sagittal T2WI without fat suppression had a TR of 3400 millisecond and a TE of 120 millisecond within a FOV of 26 cm × 26 cm. Finally, coronal and oblique axial T2WI without fat suppression were acquired with a TR of 3400 millisecond and TE of 120 millisecond, with a FOV of 20 cm × 20 cm.

Imaging features

The axial tumor length (ATL), longitudinal tumor length (LTL), ATL/LTL ratio, apparent diffusion coefficient (ADC), lymph node metastasis, and tumor circumferential resection margin (CRM) were measured and recorded. Lymph nodes with short diameters greater than 8 mm or less than 8 mm but with irregular morphology, rough edges, uneven signals, and high DWI signals were defined as positive for lymph node metastasis (+); otherwise, lymph node metastasis was defined as negative (-). When the distance between the primary tumor and malignant structures, such as metastatic lymph nodes in the mesorectum, cancer nodules, extra-rectal vascular invasion, mesorectal fascia, and adjacent structures, was less than 1 mm, the tumor was CRM-positive (+). Otherwise, it was CRM negative (-). Quantitative parameters such as the rate constant (K_{ep}), volume transfer constant (K^{trans}), volume of the extravascular extracellular space (V_e), and plasma volume fraction (V_p) were measured using the software. Relevant indicators were measured and recorded by two experienced imaging specialists. The final result is the average of two measurements. The intraclass correlation coefficient (ICC) was calculated to evaluate the reliability of the imaging results obtained by the two specialists (ICC < 0.4 is poor, 0.4-0.75 is fair, > 0.75 is good)[6].

Prognostic indicators of patients

Prognostic indicators included perioperative indicators (operation time, perioperative bleeding, first exhaust time, first defecation time, eating recovery time, and hospital stay) and postoperative complications (incision infection, anastomotic fistula, anastomotic bleeding, ileus, abdominal infection, and pulmonary infection).

Statistical analysis

Statistical analyses were performed using SPSS version 23.0. Categorical data are presented as the frequency of occurrence (n) and percentage (%). The χ^2 test was used to examine the differences in proportions between the groups. Additionally, we performed a t-test to evaluate and compare the quantitative data between the two groups. To assess the predictive value of the imaging characteristics for the outcomes of patients diagnosed with CRC, we performed receiver operating characteristic (ROC) curve analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Analysis of MRI imaging features

Among 122 cases of CRC, 22 showed low signal intensity and irregularly shaped tumor lesions, whereas the adjacent mucosa and submucosa had relatively high signal intensities. In 55 cases, alternating low and high signals of the muscle layer surrounded the tumor lesions, with the low signal of the muscle layer appearing as a complete continuous ring (of these, 46 cases of tumor lesions had rough edges or uneven signals, and nine cases of lymph nodes on MRI images showed obvious high signals). In 32 cases, the tumor signal passed through the muscular layer, and the boundary between the muscular layer and the perienteric adipose tissue was blurred (among these cases, 7 showed a high signal in the perienteric adipose tissue, which was mostly tortuous or nodular). Tumor signals were found in 13 adjacent tissues and organs, and the fat space between the adjacent tissues and organs was blurred (among these cases, three lymph nodes showed obvious high signals on MRI). Figure 1 shows the MRI findings of the patient diagnosed with rectal cancer.

In the present study, we evaluated the radiographic characteristics of patients and discovered a significant difference in the average LTL and ATL between patients with poor and good prognoses, with the former exhibiting higher values ($P < 0.05$). In addition, although we also compared ATL/LTL, lymph node metastasis, and CRM between the two groups of patients, the differences between these indicators were not statistically significant ($P > 0.05$). This finding may indicate that these parameters play a limited role in predicting the prognosis of the disease or that more in-depth research is needed in future studies to reveal their potential relationship with disease prognosis (Figures 2 and 3).

We conducted an in-depth analysis of the imaging parameters across the two patient groups to identify any potential disparities associated with varying disease prognoses. However, Kep did not show statistically significant variation

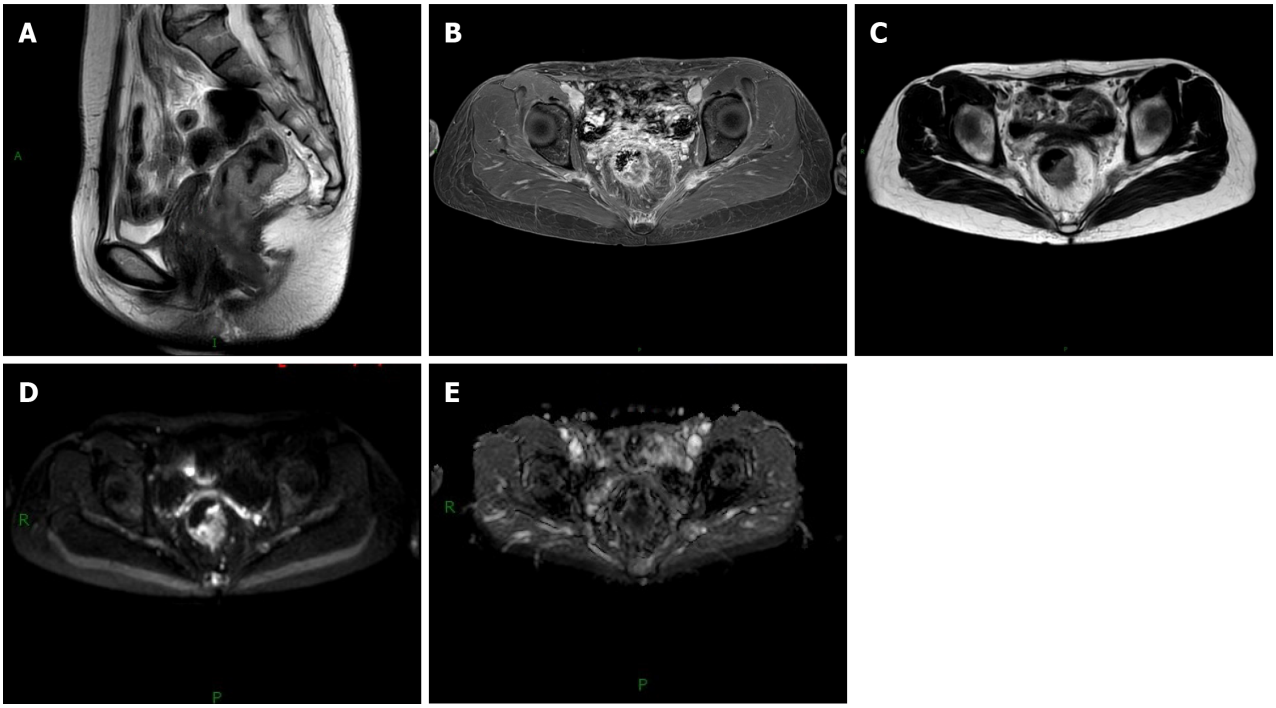

Figure 1 Images of patients with rectal cancer. A: Sagittal view showing intestinal wall thickening located approximately 7.0 cm from the anal edge, with a lesion length of approximately 3.6 cm. There is local posterior margin breakthrough of the outer membrane layer into the periintestinal fascia; B: Posterior wall of the rectum demonstrating thickening and uneven enhancement; C: T2-weighted imaging sequence revealing significant uneven thickening of the posterior rectal wall, penetrating the adventitia and invading adjacent periintestinal fascia; D: DWI sequence displaying patchy high signal intensity within the lesion; E: Corresponding apparent diffusion coefficient map indicating low signal intensity, indicative of significantly restricted diffusion.

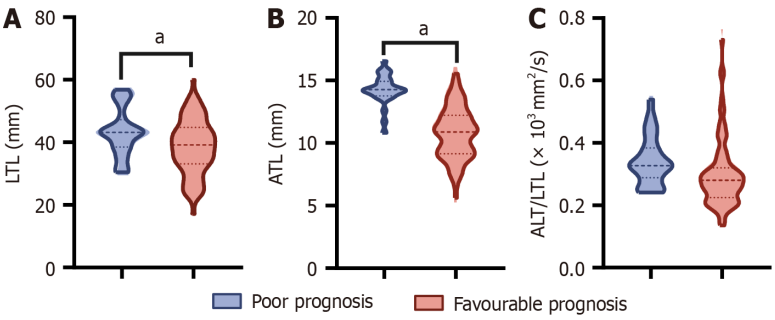

Figure 2 Longitudinal tumor length, axial tumor length, and axial tumor length/longitudinal tumor length. A: Longitudinal tumor length (LTL) of patients with colorectal cancer; B: Axial tumor length (ALT) of patients with colorectal cancer; C: ATL/LTL of patients with colorectal cancer. [a]*P* < 0.05; LTL: Longitudinal tumor length; ATL: Axial tumor length.

between the different prognostic groups ($P > 0.05$), suggesting its limited efficacy in differentiating the prognosis of patients with CRC. Nonetheless, we observed substantial differences in the other imaging parameters, specifically K^{trans}, V_e, V_p, and ADC ($P < 0.05$). These significant variations imply that these parameters may be crucial for the prognostic assessment of CRC. Figure 4 provides a visual representation of the disparities in K^{trans}, V_e, V_p, and ADC values between the two patient groups to present these findings clearly.

Prognostic indicators of patients

In our analysis of the prognostic factors in patients with CRC, we identified significant disparities in various clinical indicators related to patient outcomes. Specifically, there were pronounced differences in operation time, perioperative bleeding, first exhaust, first defecation, eating recovery period, and hospital stay between patients with contrasting prognoses ($P < 0.05$). Patients with a favorable prognosis had an average hospital stay of approximately 10.57 days, whereas those with an unfavorable prognosis experienced prolonged hospitalization, averaging 14.25 days. Furthermore, the rate of postoperative complications varied significantly between the two groups. Patients with good prognosis had an average complication rate of approximately 3.95%, whereas those with poor prognosis had a markedly higher rate of 12.64%. To illustrate these differences more vividly, Figures 5 and 6 depict the variations in the perioperative indices and complication rates among patients with different prognoses.

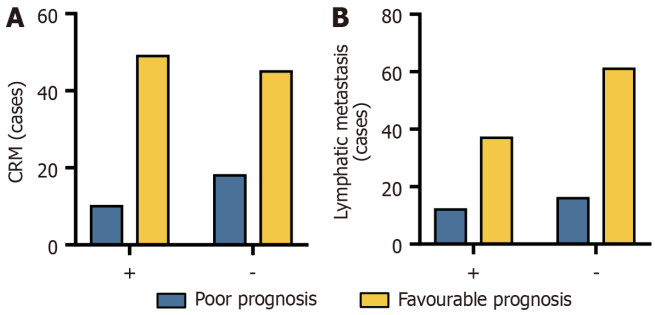

Figure 3 Circumferential resection margin and lymph node metastasis. A: The number of positive and negative circumferential resection margin in patients with colorectal cancer; B: The number of positive and negative lymph node metastases in patients with colorectal cancer. CRM: Circumferential resection margin; +: Positive; -: Negative.

Correlation between imaging features of CRC and short-term prognosis of laparoscopic radical resection

In the logistic regression analysis, the primary outcome of interest was the patient prognosis at the 30-day mark after surgery. For this analysis, a favorable outcome was recorded as '0', whereas an unfavorable outcome was recorded as '1'. The independent variables considered included LTL, ATL, ADC, K^{trans}, V_e, and V_p, all of which showed significant variance in the initial assessment of imaging features in the univariate analysis. A binary logistic regression model was constructed using these variables to examine their associations with the dependent variable. These findings indicate that LTL, ATL, ADC, K^{trans}, and V_p are predictive factors for short-term postoperative prognosis following laparoscopic radical resection. For the detailed results, please refer to Tables 1 and 2.

The ROC curve results showed that LTL, ATL, ADC, $K^{trans,}$ and V_p had predictive values for short-term prognosis of laparoscopic radical resection ($P < 0.05$), with AUC of 0.648, 0.927, 0.821, 0.809, and 0.831, respectively. The optimal cutoff value for LTL was 43.120, with a predictive sensitivity of 0.643 and specificity of 0.702 ($P = 0.017$). For ATL, the optimal cutoff value was 13.580, predictive sensitivity was 0.893, and specificity was 0.904 ($P < 0.001$). ADC had an optimal cutoff value of 0.370, with a predictive sensitivity of 0.607 and specificity of 0.883 ($P < 0.001$). K^{trans} had an optimal cutoff value of 32.090, with a predictive sensitivity of 0.714 and specificity of 0.968 ($P < 0.001$). The optimal cutoff value of V_p was 19.950, with a predictive sensitivity of 0.714 and specificity of 0.894 ($P < 0.001$). Further details are provided in Table 3 and Figure 7.

DISCUSSION

CRC is the third most prevalent malignancy globally and poses a significant threat to human health. In 2020, approximately 1.93 million individuals were diagnosed with the disease globally. The mortality rate associated with CRC is surpassed by that of lung cancer, making it the second leading cause of cancer-related deaths globally[7]. Patients often do not exhibit distinct symptoms during the initial stages of CRC development. However, as the tumor progresses and enlarges, patients may experience a growing frequency of bowel movements, a sensation of incomplete bowel evacuation, and potentially develop conditions such as intestinal narrowing or complete bowel obstruction. Additionally, it is common for patients to present with general symptoms such as diminished appetite and significant weight loss[8,9]. Clinical research indicates that nearly 85% of individuals with early-stage rectal cancer present with hematochezia as the sole clinical sign. However, these symptoms are frequently disregarded by patients, leading to delays in seeking medical intervention[10]. As imaging diagnostics continues to advance, the spatial resolution achievable using MRI technology has steadily improved. Consequently, an increasing array of functional MRI techniques are being integrated into clinical diagnostic practices[11,12].

Variations in MRI parameters can profoundly affect study outcomes, including the potential to degrade image quality and data reliability, produce artifacts and measurement errors, compromise the accuracy of tumor microvascular assessments and pathological grading predictions, diminish the reproducibility of radionic features, and modify the measurement results of the region of interest. It is imperative to control and standardize the MRI parameters strictly to ensure the precision and reliability of MRI findings. The MRI examination parameters used in this study conform to industry standards and have been meticulously optimized and adjusted by practical application and validated by a multitude of medical professionals and patients within the hospital. In this study, 22 of 122 patients with CRC showed low signal intensity and irregularly shaped tumor lesions, whereas the adjacent mucosa and submucosa showed relatively high signals. In 55 cases, low and high signals of the muscle layer alternately surrounded the tumor lesions, and the low signal of the muscle layer appeared as a complete continuous ring (among these, 46 cases of tumor lesions had rough edges or uneven signals, and 9 cases of lymph nodes on MRI images showed obvious high signals). In 32 cases, the tumor signal passed through the muscular layer, and the boundary between the muscular layer and the perienteric adipose tissue was blurred (among these, seven cases showed a high signal in the perienteric adipose tissue, which was mostly tortuous or nodular). Tumor signals were found in 13 adjacent tissues and organs, and the fat space between the adjacent tissues and organs was blurred (among these, three lymph nodes showed obvious high signals on MRI). Over the past few years, there have been significant advancements in the use of MRI for cancer, solidifying its role as an essential tool in the initial

Table 1 Variable assignment table

Index	Assignment method
LTL	Actual value entry
ATL	Actual value entry
ADC	Actual value entry
K^{trans}	Actual value entry
V_e	Actual value entry
V_p	Actual value entry

LTL: Longitudinal tumor length; ATL: Axial tumor length; ADC: Apparent diffusion coefficient; K^{trans}: Volume transfer constant; V_e: Volume of the extravascular extracellular space; V_p: Plasma volume fraction.

Table 2 Logistic regression analysis

Index	β	SE	Wald	*P* value	OR	95%CI
LTL	-0.190	0.067	8.093	0.004	0.827	0.726-0.943
ATL	1.397	0.372	14.065	< 0.001	4.042	1.948-8.386
ADC	-7.359	1.737	17.959	< 0.001	0.001	0.000-0.019
K^{trans}	0.185	0.063	8.598	0.003	1.203	1.063-1.361
V_e	-0.043	0.047	0.840	0.359	0.958	0.873-1.051
V_p	-.260	0.116	5.050	0.025	0.771	0.614-0.967

LTL: Longitudinal tumor length; ATL: Axial tumor length; ADC: Apparent diffusion coefficient; K^{trans}: Volume transfer constant; V_e: Volume of the extravascular extracellular space; V_p: Plasma volume fraction; SE: Standard error; OR: Odds ratio.

Table 3 Receiver operating characteristic curve analysis table of imaging features predicting short-term prognosis of laparoscopic radical resection

Index	AUC	Cutoff	SE	Sensitivity	Specificity	*P* value	95%CI
LTL	0.648	43.120	0.057	0.643	0.702	0.017	0.538-0.759
ATL	0.927	13.580	0.027	0.893	0.904	< 0.001	0.875-0.979
ADC	0.821	0.370	0.048	0.607	0.883	< 0.001	0.727-0.915
K^{trans}	0.809	32.090	0.061	0.714	0.968	< 0.001	0.689-0.928
V_p	0.831	19.950	0.056	0.714	0.894	< 0.001	0.721-0.940

LTL: Longitudinal tumor length; ATL: Axial tumor length; ADC: Apparent diffusion coefficient; K^{trans}: Volume transfer constant; V_p: Plasma volume fraction; AUC: Area under the curve.

staging of tumors and formulation of treatment strategies. In the context of CRC, MRI is not limited to the evaluation of primary tumors and regional lymph nodes. It plays a crucial role in risk stratification by detecting indicators of high-risk tumors such as extramural vascular invasion. Furthermore, it is instrumental in evaluating the effectiveness of neoadjuvant chemoradiotherapy[13,14]. MRI enables radiologists to delineate the precise location and contour of tumors, aid in quantifying tumor dimensions, and categorize lymph node involvement. Additionally, it can confirm the presence of vascular invasion outside the tumor and ascertain the relationship between the tumor and the adjacent anatomical structures.

Laparoscopic surgery is a prevalent and minimally invasive approach for the treatment of CRC that offers benefits such as reduced patient trauma and quicker postoperative recovery. In cases of early to moderately advanced CRC, this surgical method has the potential to achieve a complete cure[15]. Despite the effectiveness of laparoscopic procedures in enhancing patient survival rates, the risks of postoperative metastasis and tumor recurrence persist and can significantly affect patient outcomes[16]. Our study findings indicate that patients with poor prognoses had notably higher LTL and ATL measurements than those with favorable prognoses. This finding suggests that elevated LTL and ATL values

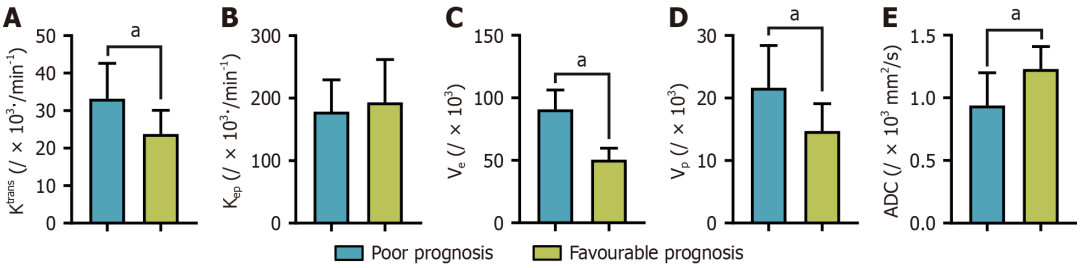

Figure 4 Comparison of imaging parameters. A: Volume transfer constant of patients with colorectal cancer; B: Rate constant of patients with colorectal cancer; C: Volume of the extravascular extracellular space of patients with colorectal cancer; D: Plasma volume fraction of patients with colorectal cancer; E: Apparent diffusion coefficient of patients with colorectal cancer. $^aP < 0.05$; K^{trans}: Volume transfer constant; K_{ep}: Rate constant; V_e: Volume of the extravascular extracellular space; V_p: Plasma volume fraction; ADC: Apparent diffusion coefficient.

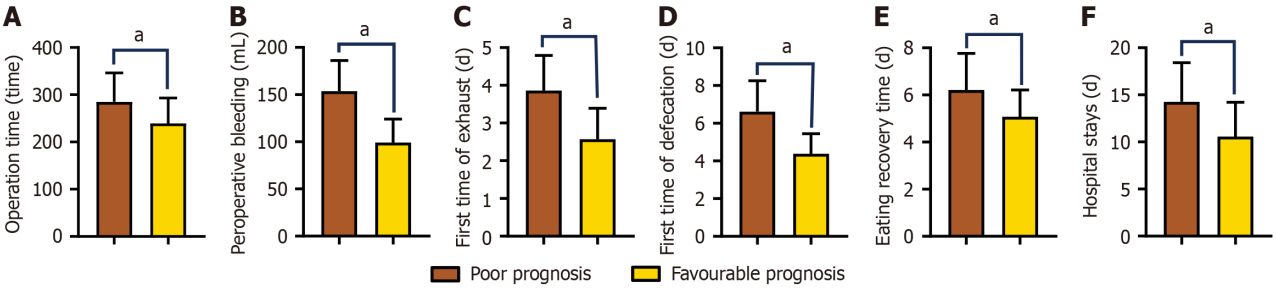

Figure 5 Perioperative-related indicators for different prognoses. A: Operation time of patients with colorectal cancer; B: Perioperative bleeding in patients with colorectal cancer; C: First time of exhaust for patients with colorectal cancer; D: First time of defecation for patients with colorectal cancer; E: Eating recovery time for patients with colorectal cancer; F: Hospital stay for patients with colorectal cancer. $^aP < 0.05$.

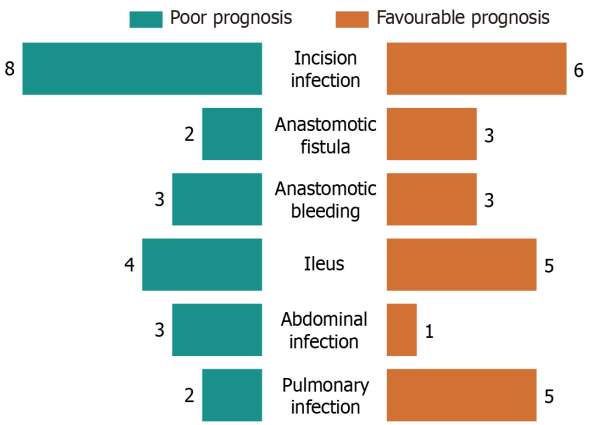

Figure 6 Comparison of postoperative complications between groups.

detected on MRI are indicative of a higher risk of unfavorable prognosis in patients with CRC. Elevated LTL and ATL levels may also reflect a more extensive tumor burden, which could be associated with rapid tumor growth and lower tumor differentiation grade, among other factors. Results of Hajibandeh *et al*[17] showed that, in patients with colon cancer, tumor size was an independent predictor of the number of harvested lymph nodes, positive lymph nodes, and lymphocytic infiltration. In tumor biology, the volume and growth rate of tumors is intrinsically linked to their proliferation. A larger tumor volume may suggest a higher tumor cell load and more complex tumor microenvironment, which can increase the complexity of surgery and extend postoperative recovery times. Tumor size is a crucial indicator of tumor cell proliferation. Increased tumor volume often implies heightened proliferation activity among tumor cells, typically associated with the invasiveness and metastatic potential of the tumor[18]. The results of Dai *et al*[19] showed that tumor size is an independent factor for overall survival and disease-free survival in patients with infiltrative colorectal adenocarcinoma. Due to potential hypoxia and inadequate nutrient supply in the central regions of the tumor, larger tumors may undergo necrosis, which can affect the tumor's response to treatment and the patient's prognosis. Furthermore, larger tumors often indicate advanced staging, leading to poorer prognosis and necessitating more complex surgical interventions. This outcome increases the risk associated with surgery and the likelihood of postoperative

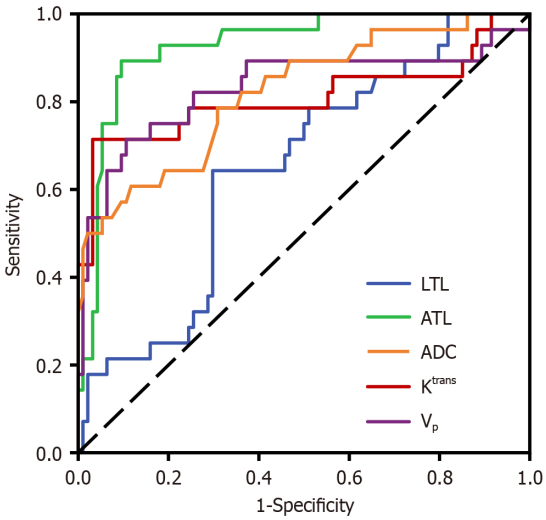

Figure 7 Receiver operating characteristic curve of imaging features for predicting short-term prognosis of laparoscopic radical resection. LTL: Longitudinal tumor length; ATL: Axial tumor length; ADC: Apparent diffusion coefficient; K^{trans}: Volume transfer constant; V_p: Plasma volume fraction.

complications, thereby affecting the short-term prognosis of patients.

Within the scope of this study, we observed that patients with a poor prognosis exhibited significantly elevated levels of K^{trans}, V_e, and V_p than those with a more favorable outcome. Conversely, the ADC values were markedly lower in the former group. Our analysis suggests that patients with CRC with a negative outlook tend to have less mature vascular development and a reduced muscular component, resulting in increased vascular permeability of the tumor. This heightened permeability allows for rapid infiltration of contrast medium into the interstitial space of the tumor. In contrast, patients with a favorable prognosis have tumor vascular permeability closer to normal levels, accounting for the relatively higher K^{trans}, V_e, and V_p values observed in patients with poor prognoses[20,21]. K^{trans} is an indicator of vascular permeability, blood flow, and microvascular density and provides insight into the rate at which the contrast agent diffuses from the vascular space into the extravascular extracellular space. Elevated K^{trans} levels indicated a higher malignant grade of the lesion. The K^{trans} value is intricately linked to tumor angiogenesis, which is the key connection between tumor growth and metastasis. Generally, higher K^{trans} values indicate increased angiogenic activity, which may affect the invasiveness of tumors and, by extension, patient prognosis[22]. Ve is a measure of the extracellular volume fraction, which represents the metabolic capacity of the contrast agent within the tumor.

Conversely, Vp signifies average vascular density and is particularly responsive to changes in perfusion within the tumor vasculature. An increase in these parameters is associated with enhanced blood perfusion to the tumor, suggesting a more aggressive tumor behavior and potentially poorer patient outcomes[23,24]. ADC quantifies the diffusion rate and extent of movement of water molecules. This result serves as a descriptor of the diffusional mobility of water molecules in various spatial orientations. The cellular density of tissue influences the ADC value. With an increase in cell density, intercellular spaces become narrow, the intracellular environment undergoes alterations, and the mobility of water molecules is constrained. This restriction leads to heightened signals in diffusion-weighted MRI scans and a corresponding decrease in ADC values[25]. The findings of this study indicate that parameters such as LTL, ATL, ADC, K^{trans}, V_e, and V_p can predict short-term outcomes after laparoscopic radical resection surgery. The areas under the ROC curves for these parameters were 0.648, 0.927, 0.821, 0.809, and 0.831, with sensitivity values of 0.643, 0.893, 0.607, 0.714, and 0.714 and specificities of 0.702, 0.904, 0.883, 0.968, and 0.894, respectively. These results suggest a correlation between imaging biomarkers and the short-term prognosis of laparoscopic radical resection. The current investigation was a retrospective analysis conducted at a single medical center, and the relatively brief follow-up period could have introduced bias into the findings. In our subsequent research, we plan to expand our approach by initiating a multicenter large-scale study involving collaboration among multiple hospitals. This plan will be complemented by long-term follow-up to establish a more robust and reliable foundation for the prognostic utility of imaging biomarkers in patients with CRC.

CONCLUSION

In our study, we analyzed the radiographic characteristics of CRC and their association with short-term outcomes in patients undergoing laparoscopic radical resection. These findings suggest that these imaging biomarkers have predictive significance and are correlated with short-term prognoses. This insight can serve as a valuable reference point for clinical decision-making and may contribute to the refinement of individualized treatment strategies. It is essential to adopt a holistic approach when applying these findings and thoroughly assessing the prognosis of each patient, considering their unique circumstances and medical histories.

FOOTNOTES

Author contributions: Fang ZH designed and performed the study and wrote the paper; Qi YG designed the study, supervised the report, and contributed to the analysis; Hao AH collected the clinical data; All authors have approved the manuscript.

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Informed consent statement: The requirement for informed consent was waived owing to the retrospective nature of the study.

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

Data sharing statement: Data can be obtained from the corresponding author upon request at 13256681970@163.com.

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Retrospective Study

Efficacy of water infusion combined with defoamers in colonoscopy

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Abstract

BACKGROUND

Currently, colonoscopy still needs continuous optimization and exploration of novel alternative approaches to enhance the experience of patients during colonoscopy.

AIM

To analyze the efficacy of water infusion combined with defoamers in colonoscopy.

METHODS

This study included 97 patients undergoing colonoscopy from January 2024 to June 2024. The participants were categorized into two groups, namely, the control group (n = 47), who underwent conventional colonoscopy, and the experimental group (n = 50), who received colonoscopy using water injection combined with defoamers. A comparative analysis was then conducted on the disease detection rate (colonic polyps, colonorrhagia, colonic ulcers, colonic mucosal lesions, and others), colonoscopy duration, abdominal pain [visual analog scale (VAS)], Boston bowel preparation scale (BBPS), self-rating anxiety scale (SAS), bowel preparation comfort, complications (intestinal perforation, bleeding, nausea and vomiting, abdominal pain, and abdominal distension), and patient satisfaction.

RESULTS

The experimental group demonstrated a significantly higher total disease detection rate, BBPS scores, and patient satisfaction compared with the control group. Further, the research group exhibited shorter colonoscopy duration, lower VAS and SAS scores and total complication rate, and better patient comfort and

satisfaction.

CONCLUSION
These results indicate that the combination of water injection and defoamers exhibited an overall better therapeutic effect than conventional colonoscopy, mainly reflected in higher disease detection rate, faster examination efficiency, lower abdominal pain, anxiety, and complication incidences, and significantly better bowel preparation, comfort, and patient satisfaction.

Key Words: Water injection; Defoamer; Colonoscopy; Curative effect; Visual analog scale

Core Tip: Continuous innovation and exploration of new alternative solutions for colonoscopy remain essential to improve patients' colonoscopy experience. This study proposes the application of the water-infusion method combined with defoamers in colonoscopy and compares it with the traditional colonoscopy approach to validate its clinical superiority in colonoscopy. We revealed that the water-infusion method combined with defoamers for patients undergoing colonoscopy demonstrates more clinical advantages compared with the air-infusion method, manifested as substantially higher disease detection rates and examination efficiency, a significant reduction in patients' discomfort and anxiety levels, an improvement in the effectiveness of bowel preparation and patient comfort, and a favorable safety profile. Our research results provide additional alternatives for ameliorating the medical experiences of patients undergoing colonoscopy.

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INTRODUCTION

Colonoscopy is intuitive and effective for the clinical assessment of colon polyps, colonorrhagia, colon ulcers, colonic mucosal lesions, and various other intestinal diseases[1,2]. This examination method utilizes a flexible colonoscope with an approximately 1-cm diameter to extend from the patient's anus into the rectum and then the colon to observe any abnormalities in the colon[3]. Colonoscopy exhibits certain clinical advantages, but it is essentially an invasive procedure that inevitably brings discomfort and adverse experiences to patients[4,5]. Painless endoscopy minimizes patient discomfort but may cause postoperative pain and bloating, as well as an elevated risk of serious complications if sedative intervention is utilized[6,7]. Therefore, continuous innovation and investigation of new alternatives are still required to improve the colonoscopy experience of patients.

Conventional colonoscopy with the air insufflation method mainly involves intestinal cavity exposure through air insufflation and using the axial shortening technique to introduce the endoscope, followed by body position changes, abdominal compressions, and other ways to achieve colonoscopy[8,9]. However, this approach induces strong intestinal stimulation, causing discomfort due to colon expansion after inflation, as well as the possibility of subsequent looping that may hinder cecal insertion[10]. The present study proposed water injection combined with defoamers to improve the above situation, considering the currently limited research in this field. Unlike air insufflation, water injection is an intervention that reduces the air injection while taking advantage of the characteristics of the water to flow from the lower colon to the lower position, thereby decreasing the intestinal dilatation and the difficulty of endoscope passage by reducing the sigmoid colon curvature[11,12]. Further, this test is beneficial to reduce the risk of loop formation, greatly shortening the assessment duration and relieving discomfort, including abdominal distension and pain[13]. Defoamers improve visibility during colonoscopy and provide a clearer field of vision during the inspection, thereby minimizing undesirable disturbances (foam or mucus, *etc*.) in the patient's body and helping to improve the examination efficiency [14,15]. The defoamers typically used in colonoscopy include simethicone, dimethicone, and dyclonine hydrochloride mucilagines in clinical practice. Notably, simethicone represents a compound of dimethicone and silicon dioxide, with a significantly better defoaming capacity than that of dimethicone. Moreover, it entails a lower usage cost when compared to dyclonine hydrochloride mucilagines[16]. Hence, the present study selected simethicone as the defoaming agent for the clinical analysis.

In this study, we proposed the use of water injection combined with defoamers in colonoscopy and compared it with conventional colonoscopy, to confirm its clinical advantages and provide more options for improving the medical experience of patients undergoing colonoscopy.

MATERIALS AND METHODS

Baseline data

This retrospective study included 97 patients undergoing colonoscopy in Nanhai Family Practice Hospital (Nanhai Guicheng Hospital) from January 2024 to June 2024. The participants were categorized into the control group (n = 47), who underwent conventional colonoscopy, and the experimental group (n = 50), who received colonoscopy with water injection and defoamers.

Eligibility and exclusion criteria

Inclusion criteria: All patients met the colonoscopy indications, with complete medical records and normal understanding and expression abilities.

Exclusion criteria: Patients with a colorectal surgery history, digestive tract obstruction or perforation risk, active gastrointestinal bleeding, severe heart, lung, and kidney dysfunction, psychological illness, or mental disturbance, as well as pregnant women.

Treatment methods

All participants were routinely placed in the left lateral decubitus position. Compound tetracaine gel was applied to the anus and the anterior part of the endoscope for local anesthesia and lubrication before the procedure. The same experienced endoscopist single-blindly performed all examinations. Both groups were assessed with ELUXEO 7000 electronic colonoscopy. The control group underwent a conventional colonoscopy, with conventional air as the injected gas. The experimental group underwent colonoscopy with water injection combined with defoamers. The defoamer, simethicone of 10 mL, was placed in a container and added to the warm water of 70 mL (approximately 40 °C) to prepare a unit of 80-mL solution after repeated stirring. The patient was instructed to administer it orally 20 minutes preoperatively. Posture rotation was then performed in the following order: (1) Supine position; (2) Left lateral position; (3) Prone position; and (4) Right lateral position, with each posture maintained for 5 minutes. Upper abdomen massage was then performed simultaneously. The endoscope special flushing pump was disinfected and placed in warm water controlled at 37 °C. The water injection end was then inserted into the biopsy hole of the endoscope, and a foot turn was utilized for water injection, which did not affect the colonoscopy procedure. The endoscope insertion method was the same as that of the conventional colonoscopy, adopting the method of "entering the endoscope along the cavity and shortening the longitudinal axis". The difference was that the air insufflation pump was turned off, and the air insufflation was changed to a warm water (constant temperature: 37 °C) injection. The sewage was sucked out and clean warm water was injected to clear the vision field for easy endoscope insertion in case of residual sewage from the intestine that affected the visual field. The air retained in the intestine was sucked out at any time during the insertion to reduce bending and angularity, making the endoscope insertion easier.

Analysis indexes

The disease detection rate (colonic polyps, colonorrhagia, colonic ulcers, colonic mucosal lesions, and others), colonoscopy duration, abdominal pain [visual analog scale (VAS)], Boston bowel preparation scale (BBPS), self-rating anxiety scale (SAS), bowel preparation comfort, complications (intestinal perforation, bleeding, nausea and vomiting, ab-dominal pain, and abdominal distension), and patient satisfaction were comparatively analyzed.

Disease detection rate: This study recorded the detection rates of colonic polyps, colonorrhagia, colonic ulcers, colonic mucosal lesions, and other diseases.

Colonoscopy duration: The colonoscopy duration was observed and recorded in both groups.

Abdominal pain degree: The abdominal pain level of the participants before and after the intervention was evaluated with the VAS. The score, ranging from 0 point to 10 points, is positively correlated with the pain degree.

Bowel preparation effect: The bowel preparation effect was evaluated with the BBPS (total score: 9). A higher score indicates a better bowel preparation effect.

Psychological status: We utilized the SAS, a 20-item tool of subjective anxiety feelings scored based on the standard of 1, 2, 3, and 4, to assess patients' psychological status. The score is proportional to the patient's anxiety.

Bowel preparation comfort: The bowel preparation comfort level was compared with the VAS, with 0-4 points, 5-6 points, 7-8 points, and 9-10 points denoting mild, moderate, severe, and extremely severe discomfort, respectively.

Complications: The number of adverse events, including intestinal perforation, bleeding, nausea and vomiting, abdominal pain, and abdominal distension, were observed and recorded. Further, the total postoperative complication rate was calculated.

Patient satisfaction: Patient satisfaction was measured with the department's self-made bowel preparation satisfaction scale (full score: 100 points) and compared between the two groups. The score was judged as very satisfied (≥ 80 points), relatively satisfied (60–79 points), and dissatisfied (≤ 60 points). A higher score indicates higher patient satisfaction.

Statistical analysis

The measurement data were statistically expressed as the mean ± SE of the mean. The one-sample Kolmogorov–Smirnov test for normality and Levene's test were used to assess the normality and homoscedasticity of the measurement data, respectively. A two-independent sample *t*-test was implemented for each parameter if the data complied with a normal distribution. Conversely, the Mann–Whitney *U* test was used. Count data were presented as ratios (percentages), and the between-group comparisons were conducted with χ^2 tests. Data were analyzed with Statistical Package for the Social Sciences version 18.0, with the statistical difference level set at *P*-values of < 0.05.

RESULTS

Baseline data

Similar baseline data (*e.g.*, sex, age, height, weight, disease course) were determined between the control and experimental groups ($P > 0.05$) (Table 1).

Comparative analysis of disease detection rates

The experimental group demonstrated a higher total detection rate of colonic polyps, colonorrhagia, colonic ulcers, colonic mucosal lesions, and other diseases than the control group ($P < 0.05$) (Table 2).

Comparative analysis of colonoscopy duration and various scale scores

The experimental group demonstrated shorter colonoscopy duration, lower VAS and SAS scores, and higher BBPS scores than the control group ($P < 0.05$) (Figure 1).

Comparative analysis of bowel preparation comfort

Bowel preparation comfort was significantly better in the experimental group than in the control group ($P < 0.05$) (Table 3).

Comparative analysis of complication incidences

The experimental group exhibited a lower overall incidence of intestinal perforation, bleeding, nausea and vomiting, abdominal pain, and abdominal distension than the control group ($P < 0.05$) (Table 4).

Comparative analysis of patient satisfaction

Higher patient satisfaction was identified in the experimental group compared with the control group ($P < 0.05$) (Table 5).

DISCUSSION

Colonoscopy, as the gold standard for diagnosing intestinal lesions, exhibits the advantages of easy operation and little effects on the gastrointestinal tract[17]. However, the efficiency and safety of colonoscopy depend on the bowel preparation degree to some extent[18]. Adequate bowel preparation not only helps to ensure smooth colonoscopy and shorten inspection time but also improves the high-quality detection rate and safety, thereby minimizing patient discomfort[19,20]. Therefore, effective and adequate intestinal preparation is crucial for patients undergoing colonoscopy.

In this study, we first assessed the disease detection rate and revealed that the experimental group demonstrated a higher overall detection rate for colon polyps, colonorrhagia, colon ulcers, colonic mucosal lesions, and other intestinal diseases, indicating that water injection combined with defoamers improved the disease detection rate in colonoscopy. Bai *et al*[21] revealed that the defoamer simethicone applied to colonoscopy significantly improved the adenoma detection rate, similar to our research results. Second, the experimental group exhibited a shorter colonoscopy duration, lower VAS and SAS scores, and higher BBPS scores, indicating that water injection combined with defoamers in colonoscopy is not only beneficial to improve colonoscopy efficiency, but also reduces abdominal pain, relieves patients' anxiety, and improves bowel preparation. This may be because defoamers alter the surface tension of bubbles and promote bubble decomposition, causing a good bubble clearance in the intestine, which is conducive to improving the inspection efficiency, lesion detection rate, and adequate bowel preparation[22,23]. Wu *et al*[24] emphasized the effectiveness of the supplementary use of simethicone before endoscopy in improving the small intestine visualization by reducing bubbles in the colon cavity. Further, we observed more advantages in the experimental group in terms of bowel preparation comfort, indicating that water injection combined with defoamers helps improve the intestinal preparation comfort of patients undergoing colonoscopy to some extent. The total incidence of complications, such as intestinal perforation, bleeding, nausea and vomiting, abdominal pain, and abdominal distension, was significantly lower in the experimental group than in the control group. This indicates that water injection combined with defoamers is safe and tolerable for patients undergoing colonoscopy, which help patients reduce the risk of complications. This may be because nitrogen accounts for the vast majority of the air injected into the patient's intestines during conventional colonoscopy and is difficult to be absorbed by the body or safely metabolize, causing the retention of a large amount of air in the intestinal cavity, thereby inducing abdominal pain, abdominal distention, and other complications[25]. Water injection combined with defoamers helps to reduce air retention in the intestinal cavity. Moreover, defoamers are safer because they are not

Table 1 Baseline information, *n* (%)

Variables	Control group (*n* = 47)	Experimental group (*n* = 50)	χ^2/t	*P* value
Sex			0.227	0.634
Male	25 (53.19)	29 (58.00)		
Female	22 (46.81)	21 (42.00)		
Age (years)	49.26 ± 10.30	49.82 ± 12.24	0.243	0.809
Height (cm)	167.51 ± 9.27	168.28 ± 14.42	0.311	0.757
Weight (kg)	56.79 ± 10.94	61.76 ± 15.30	1.830	0.070
Course of disease (months)	6.55 ± 1.40	7.02 ± 1.48	1.604	0.112

Table 2 Comparative analysis of the disease detection rate, *n* (%)

Variables	Control group (*n* = 47)	Experimental group (*n* = 50)	χ^2	*P* value
Colon polyps	12 (25.53)	14 (28.00)		
Colonorrhagia	7 (14.89)	9 (18.00)		
Colonic ulcers	5 (10.64)	6 (12.00)		
Colonic mucosal lesions	2 (4.26)	4 (8.00)		
Others	6 (12.77)	11 (22.00)		
Total	32 (68.09)	44 (88.00)	5.665	0.017

Table 3 Comparative analysis of bowel preparation comfort, *n* (%)

Variables	Control group (*n* = 47)	Experimental group (*n* = 50)	χ^2	*P* value
Mild discomfort	16 (34.04)	35 (70.00)	12.563	< 0.001
Moderate discomfort	28 (59.57)	15 (30.00)	8.586	0.003
Severe discomfort	2 (4.26)	0 (0.00)	2.172	0.141
Extremely severe discomfort	1 (2.13)	0 (0.00)	1.075	0.300

Table 4 Comparative analysis of the incidence of complications, *n* (%)

Variables	Control group (*n* = 47)	Experimental group (*n* = 50)	χ^2	*P* value
Intestinal perforation	2 (4.26)	0 (0.00)		
Bleeding	1 (2.13)	0 (0.00)		
Nausea and vomiting	2 (4.26)	2 (4.00)		
Abdominal pain	2 (4.26)	1 (2.00)		
Abdominal distension	2 (4.26)	0 (0.00)		
Total	9 (19.15)	3 (6.00)	3.864	0.049

irritating and have relatively less effect on the gastrointestinal tract after being taken by the human body[26]. Moolla *et al* [27] revealed that defoamers used in colonoscopy are beneficial in reducing the risk of abdominal distension, significantly improving colon cleanliness, and increasing adenoma detection rates, which supports our results. Finally, the experimental group demonstrated higher patient satisfaction compared to the control group indicating that the combination of water injection and defoamers is beneficial for improving patient satisfaction during colonoscopy, while indirectly improving the experience for patients receiving this examination method.

Table 5 Comparative analysis of patient satisfaction, *n* (%)

Variables	Control group (*n* = 47)	Experimental group (*n* = 50)	χ^2	*P* value
Very satisfied	17 (36.17)	22 (44.00)		
Satisfied	19 (40.43)	24 (48.00)		
Dissatisfied	11 (23.40)	4 (8.00)		
Overall satisfaction	36 (76.60)	46 (92.00)	4.398	0.036

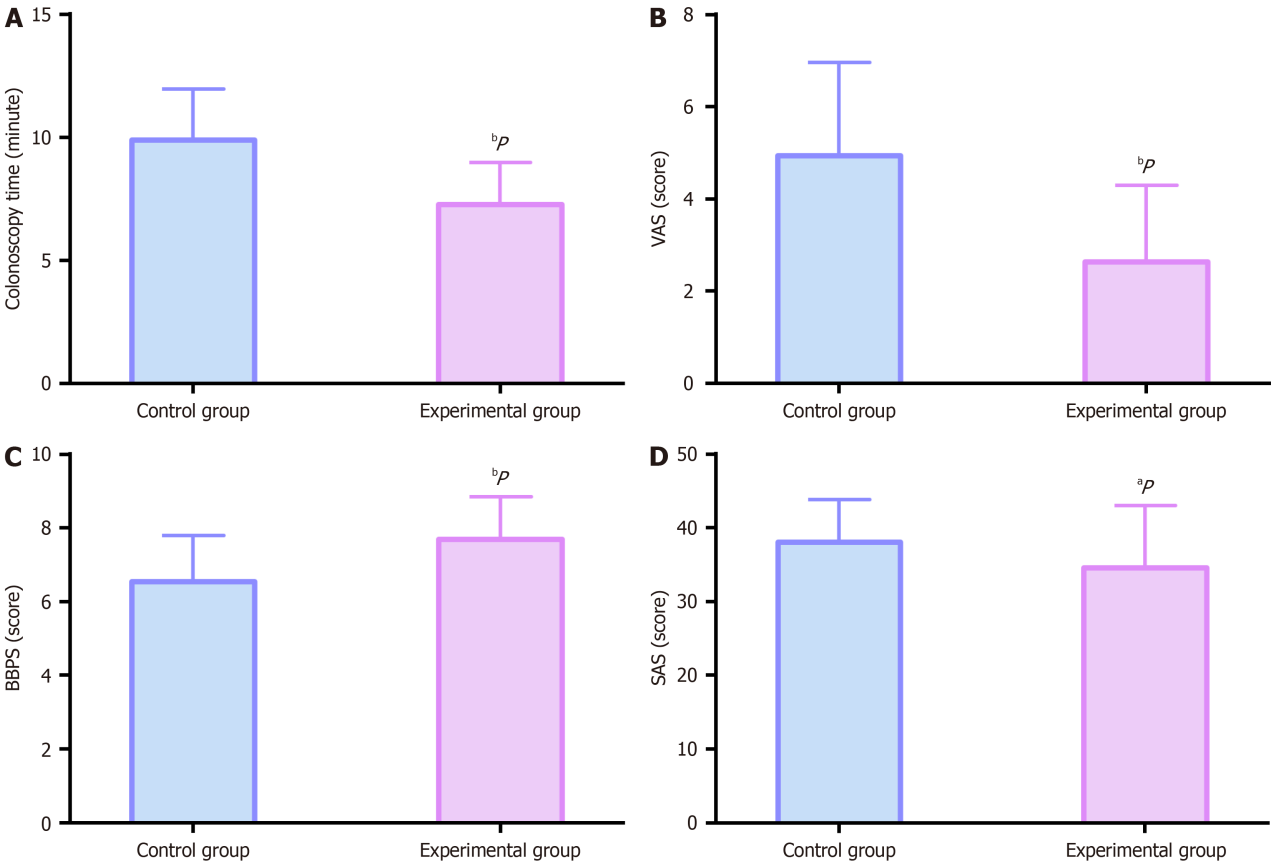

Figure 1 Comparative analysis of the duration of colonoscopy and various scale scores. A: The experimental group had a markedly shorter duration of colonoscopy; B: The visual analogue scale score was even lower in the experimental group; C: The Boston bowel preparation scale score was statistically lower in the experimental group; D: The self-rating anxiety scale score of the experimental group was notably higher. $^aP < 0.05$ and $^bP < 0.01$ compared with the control group. BBPS: Boston bowel preparation scale; SAS: Self-rating anxiety scale; VAS: Visual analogue scale.

CONCLUSION

The above research results indicate that water injection combined with defoamers for patients undergoing colonoscopy demonstrates more clinical advantages compared with air insufflation, resulting in improved disease detection and examination efficiency, significantly reduced patient discomfort and anxiety, and markedly better bowel preparation effects and comfort, with a favorable safety profile and high popularity among patients.

FOOTNOTES

Author contributions: Li J designed the study and wrote the manuscript; Li J and Chen JP collected and analyzed the data; Li J and Lai CH revised the manuscript; Li J, Fu L and Ji Y participated in collection of the data; all authors approved the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Enhanced recovery after surgery-based evidence-based care plus ice stimulation for thirst management in convalescent patients following digestive surgery under general anesthesia

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Abstract

BACKGROUND

Thirst management in convalescent patients recovering from a digestive surgery performed under general anesthesia requires attention. A simple, practical, and safe method can effectively relieve thirst symptoms in such patients.

AIM

To evaluate the enhanced recovery after surgery (ERAS)-based evidence-based care (EBC) plus ice stimulation therapy for thirst management of convalescent patients following digestive surgery performed under general anesthesia.

METHODS

A total of 191 patients convalescing after digestive surgery performed under general anesthesia between March 2020 and February 2023 and experiencing thirst were selected. In total, 89 patients and 102 patients in the control and research groups received routine care and ERAS-based EBC plus ice stimulation therapy, respectively. The following data were comparatively analyzed: (1) Thirst degree (thirst intensity numerical rating scale) and thirst distress (TD) degree (TD scale); (2) Oral mucosal wetness; (3) Unstimulated whole salivary flow rate (UWSFR); (4) Adverse reactions (palpitation, fatigue, chapped lips, and nausea and vomiting); and (5) Nursing satisfaction.

RESULTS
After nursing, thirst degree and distress were statistically lower in the research group than in the control group. Additionally, compared with the control group, the research group exhibited a lower degree of oral mucosal wetness, higher UWSFR, fewer adverse reactions, and more total nursing satisfaction.

CONCLUSION
ERAS-based EBC plus ice stimulation therapy can effectively alleviate thirst in convalescent patients recovering from a digestive surgery performed under general anesthesia. It can alleviate xerostomia symptoms, reduce adverse reactions, and improve patient comfort.

Key Words: Enhanced recovery after surgery; Evidence-based care; Ice stimulation therapy; Convalescent patients; Digestive surgery; General anesthesia; Thirst

Core Tip: After a digestive surgery performed under general anesthesia, thirst management in patients during the recovery phase requires great attention because patients who underwent such surgical procedures typically require an extended duration to revert to feasible and normal water consumption. This study aims to analyze the application of evidence-based care (EBC), based on enhanced recovery after surgery (ERAS), in conjunction with ice stimulation therapy, to address thirst management in convalescent patients who underwent digestive surgery under general anesthesia. A comprehensive analysis was performed to investigate various factors including degree of thirst, degree of thirst distress, wetness of the oral mucosa, unstimulated whole salivary flow rate, adverse reactions, and nursing satisfaction. Reportedly, ERAS-based EBC plus ice stimulation therapy effectively alleviated thirst severity experienced by patients convalescing after a digestive surgery performed under general anesthesia, ameliorated xerostomia symptoms, diminished adverse reactions, and augmented patient comfort. Moreover, the study furnished valuable clinical evidence concerning the prophylaxis and thirst treatment after digestive surgery under general anesthesia.

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INTRODUCTION

Thirst is a natural response to the body's sense of need to replenish water content. After surgery under general anesthesia, several patients experience varying degrees of thirst, primarily caused by prolonged fasting and water prohibition before and after surgery, endotracheal intubation during surgery, and anesthetic drugs[1]. Water consumption is a natural and an effective way to quench thirst; however, nurses often prohibit postoperative eating and drinking for patient safety, which blocks the required water intake and increases postoperative thirst[2,3]. To combat thirst symptoms in such cases, cotton swabs, dipped in water, are frequently used in clinical practice to moisten the patients' lips and mouth. However, this moistens only a limited area and leads to easy shedding of cotton wool on the swab[4]. Therefore, simple, practical, and safe means are required to effectively relieve thirst symptoms. Thirst management in patients recovering from digestive surgeries performed under general anesthesia requires increased attention because such patients often require a long time to recover to a state of normal water consumption.

Enhanced recovery after surgery (ERAS) combines multidisciplinary knowledge and multiple modes of care for accelerating patient recovery by optimizing several perioperative care measures that reduce the stress response of surgery [5]. To achieve this goal and enhance the effectiveness of nursing, evidence-based care (EBC) uses scientific methods and evidence-based questions to collect nursing evidence and formulated scientific preventive measures for ameliorating adverse events catered to patient-specific needs and clinical experiences[6]. Thirst is a common and an uncomfortable issue experienced by several intensive care unit (ICU)-treated patients. The common clinical practice of using oral swabs and ice water sprays effectively reduces thirst and xerostomia symptoms[7]. Ice stimulation therapy uses low temperatures generated by spraying ice water and ice gargling to stimulate specific receptors in the oropharynx, which are known as transient receptor potential melastatin 8 on cold sensory receptors. When rapidly activated, these receptors present on the oral mucosa upon stimulation by ice and open a transient receptor potential channel[8], enhancing patient comfort and satisfaction and remarkably reducing the degree of thirst experienced by the patients, ultimately reducing their thirst-induced distress[9]. Reportedly, perioperative thirst is an intense discomfort experienced by patients immediately after surgery and is associated with high morbidity; additionally, providing patients with ice stimulation (popsicles) as a part of perioperative care can effectively alleviate thirst intensity[10].

This study included 191 patients who were convalescing after a digestive surgery performed under general anesthesia and comparatively analyzed the clinical effectiveness of ERAS-based EBC plus ice stimulation therapy for managing postoperative thirst in these patients and validating the clinical advantages of this combination therapy.

MATERIALS AND METHODS

General data

This retrospective study included 191 patients convalescing after a digestive surgery performed under general anesthesia between March 2020 and February 2023 and experienced thirst. The control and research groups included 89 cases and 102 cases of routine care and ERAS-based EBC plus ice stimulation therapy, respectively; both groups were clinically comparable regarding general information ($P > 0.05$).

Inclusion and exclusion criteria

Patients convalescing from digestive surgery performed under general anesthesia and experiencing thirst; who were > 18 years old, nonmechanically ventilated, and willing to accept the nursing method; with no history of audio-visual diseases.

However, patients with insufficient volume of jugular vein filling as indicated by ultrasound determination; oral diseases; history of clinically diagnosed xerostomia, diabetes insipidus, and other diseases causing abnormal fluid volume and thirst; unstable blood pressure, heart rate, and other vital signs and chronic diseases; and inability to cooperate with the investigation were excluded.

Nursing intervention measures

The control group received routine care interventions: Ward temperature (22 °C - 24 °C) and humidity (50%-60%) were maintained within the normal range. The members of the research team were provided with cotton swabs dipped in warm indoor water (maintained at 22 °C - 27 °C) to moisten the lips and mouths of the patients. Next, lip balm was applied to patients' lips to prevent dryness. These care measures were serially performed seven times a day—three times in the morning and four times in the afternoon—with an interval of 1 hour between consecutive care sessions to ensure that the patients had sufficient time to relax. Moreover, to ensure that the patients could enjoy a peaceful lunch break, a 2-hour interval was arranged between the third and fourth nursing sessions. After each session, the used articles were promptly collected and disposed of owing to hygiene.

The research group received ERAS-based EBC plus ice stimulation therapy. Standard nursing protocol was followed, the room temperature and humidity were maintained at 22 °C - 24 °C and 50%-60%, respectively. A special elephant trunk-shaped spray nozzle (specification: (1) 30 mL; and (2) Material: Food-grade Pickering emulsion) connected to a spray bottle filled with ice sterilization water (0 °C - 6 °C) was used[11]. During the ice stimulation therapy, the spray nozzle was inserted deep into the patient's mouth, and ice water was sprayed in the following order: (1) Upper jaw; (2) Left cheek; (3) Tongue surface; (4) Right cheek; and (5) Throat. Each area was sprayed three times to ensure sufficient moisture. After spraying ice water, lip balm was applied to the patients' lips to keep them moisturized. While spraying iced water, the amount of liquid sprayed was controlled at approximately 0.1 mL, and the total amount of liquid in the entire spraying process was maintained at approximately 1.5 mL. During the nursing procedure, the patients' vital signs were closely monitored to ensure their safety and comfort. Care measures were repeated seven times a day—thrice in the morning and four times in the evening. A 1-hour interval was maintained between consecutive sessions to ensure sufficient rest time. Similarly, to prevent disturbances during the patients' lunch breaks, a 2-hour interval was arranged between the third and fourth operations. After each nursing operation, the used items were promptly disposed of to keep the environment clean and tidy.

Analysis indexes

Thirst degree and distress: The thirst intensity numerical rating scale (TINRS) was used to quantitatively evaluate thirst degree. TINRS is a straight line divided into 10 equal parts, each marked with a number ranging from 0 (no thirst) to 10 (extreme thirst) that represent different levels of thirst sensation. The patient was required to select a corresponding number representing their thirst level. A 10-point scoring system, the thirst distress (TD) scale was used for evaluating the degree of distress experienced by the patient because of thirst. A score of 0 indicates a lack of distress, whereas a score of 10 indicates a state of extreme discomfort experienced by the patient. The evaluator can directly question the patients regarding their thirst and distress, and based on the patients' response and facial expressions, assign a score. A higher score indicated a greater distress.

Oral mucosal wetness: The wetness of the patients' lips, tongue, and oral mucosa were examined to determine oral mucosal wetness, which was graded as follows: (1) 1 point, moist lips and mouth; (2) 2 points, dry lips but a moist mouth; (3) 3 points, dry lips and mouth; and (4) 4 points, peeling and chapped lips, in addition to dryness and paling of the mouth inside. This score reflects the degree of mouth moistness to assess possible thirst or other oral problems.

Unstimulated whole salivary flow rate: The cotton swab method was used to measure the unstimulated whole salivary flow rate (UWSFR) of patients. The specific operations were as follows: The saliva in the oral cavity was initially absorbed with cotton balls. Three preweighed dry cotton swabs were positioned in the patient's mouth—one under the patient's tongue and other two at the parotid glands on both sides. The patient was instructed to refrain from swallowing for 2 min, after which the cotton swabs were removed. The saliva on the patient's tongue surface was again cleaned, and

cotton swabs were reweighed. Their original weight was subtracted and the resulting weight was divided by 2 to get the patient's UWSFR (in mg/minute).

Adverse reactions: The frequency of adverse reactions, such as palpitations, fatigue, chapped lips, and nausea and vomiting, was observed and recorded for evaluation.

Nursing satisfaction: A hospital-generated 100-point nursing satisfaction survey questionnaire was circulated among the patients to obtain feedback regarding nursing satisfaction. A score of ≥ 90 indicated "very satisfied", 60-89 indicated "satisfied", and < 60 indicated "dissatisfied". Total satisfaction is the sum of very satisfied and satisfied as a percentage of the total number of cases.

Statistical analysis

Statistical Package for the Social Sciences 22.0 was used for all statistical analyses. The measurement and count data have been presented concerning the means ± SD and the number of cases (n) and percentage (%). Two independent samples, t-test and χ^2 test, were applied to the measurement and count data for identifying inter-group differences, with $P < 0.05$ as the statistical threshold.

RESULTS

Comparative analysis of general information

The research and control groups matched with respect to age, weight, comorbidities, number of surgical procedures involved, and habitual water intake ($P > 0.05$) (Table 1).

Comparative analysis of TINRS and TD scores before and after nursing

The research and control groups exhibited equivalent TINRS and TD scores before receiving care ($P > 0.05$) (Figure 1); The TINRS and TD scores of both groups decreased after nursing, with the scores of the research group being lower than the control group ($P < 0.05$).

Comparative analysis of oral mucosal wetness before and after nursing

The oral mucosal wetness scores before care did not demonstrate any significant inter-group differences ($P > 0.05$). After receiving care, the oral mucosal wetness scores of both groups statistically decreased and were lower in the research group ($P < 0.05$) than the control group (Figure 2A).

Comparison of UWSFR before and after nursing

Both groups had similar UWSFRs before receiving care ($P > 0.05$) (Figure 2B); the UWSFRs of both groups statistically increased after care and were higher in the research group than in the control group ($P < 0.05$).

Comparative analysis of adverse reactions

An analysis of the number and percentage of cases of palpitations, fatigue, chapped lips, and nausea and vomiting in the two groups indicated that the total incidence of adverse reactions was lower in the research group (3.92%), compared with the control group (24.72%, $P < 0.05$) (Table 2).

Comparison of nursing satisfaction after care

The inter-group comparison revealed that the overall nursing satisfaction was higher in the research group (95.10%) than the control group (69.66%), with a statistical significance of $P < 0.05$ (Table 3).

DISCUSSION

Digestive surgeries are typically performed under general anesthesia for various surgical needs[12]. However, before receiving general anesthesia, patients fasted and abstained from ingesting any fluids pre-operatively and post-operatively, leading to prolonged inactivity of the digestive system and reduced secretion of digestive fluids and saliva [13,14]. Meanwhile, blood loss and cell dehydration during digestive surgeries can lead to hypovolemia, hemoconcentration, and increased plasma osmotic pressure, eventually leading to thirst[15]. Thirst causes discomfort in patients and enhances their stress responses, oxygen consumption, and metabolic burden, triggering negative emotions such as anxiety and irritability, affecting patient treatment and nursing compliance, and resulting in responses such as tube biting and unplanned extubations[16,17]. This study proposes ERAS-based EBC plus ice stimulation therapy and verifies its potential advantages in combating thirst experienced by patients undergoing digestive surgery under general anesthesia to provide useful clinical evidence for the prevention and treatment of thirst after surgeries conducted under general anesthesia.

By optimizing nursing procedures and controlling stress reactions, ERAS helps patients undergoing digestive surgeries under general anesthesia recover quickly and safely[18]. Herein, the evidence-based medicine was used as basis to ensure

Table 1 Comparative analysis of general data, *n* (%)

Indicators	Research group (*n* = 102)	Control group (*n* = 89)	χ^2/t	*P* value
Age (years)	48.51 ± 3.56	47.62 ± 3.44	1.751	0.082
Weight (kg)	58.59 ± 4.37	58.81 ± 5.62	0.304	0.762
Sex			1.998	0.158
Male	54 (52.94)	38 (42.70)		
Female	48 (47.06)	51 (57.30)		
Comorbidities			0.582	0.445
Hypertension	41 (40.20)	31 (34.83)		
Diabetes mellitus	61 (59.80)	58 (65.17)		
Number of surgical procedures involved (item)			1.163	0.281
1-2	64 (62.75)	49 (55.06)		
3-4	38 (37.25)	40 (44.94)		
Habitual water intake (mL)			2.060	0.560
≤ 500	22 (21.57)	20 (22.47)		
501-1500	35 (34.31)	23 (25.84)		
1501-2500	31 (30.39)	29 (32.58)		
≥ 2501	14 (13.73)	17 (19.10)		

Table 2 Comparative analysis of adverse reactions, *n* (%)

Indicators	Observation group (*n* = 102)	Control group (*n* = 89)	χ^2	*P* value
Palpitations	1 (0.98)	3 (3.37)		
Fatigue	2 (1.96)	6 (6.74)		
Chapped lips	0 (0.00)	9 (10.11)		
Nausea and vomiting	1 (0.98)	4 (4.49)		
Total	4 (3.92)	22 (24.72)	17.481	< 0.001

Table 3 Comparison of nursing satisfaction after care, *n* (%)

Indicators	Research group (*n* = 102)	Control group (*n* = 89)	χ^2	*P* value
Very satisfied	58 (56.86)	19 (21.35)		
Satisfied	39 (38.24)	43 (48.31)		
Dissatisfied	5 (4.90)	27 (30.34)		
Total satisfaction	97 (95.10)	62 (69.66)	22.051	< 0.001

that nursing measures were scientifically validated, thereby improving nursing efficacy[19]. Moreover, EBC uses a rigorous and logical methodology, enabling us to accrue diverse information and evidence, accurately identify problems, and propose practical and effective solutions[20,21]. Thirst is a painful sensation experienced by patients following digestive surgery under general anesthesia. The timely resolution of thirst-related physiological problems is a concrete manifestation of effective nursing[22]. The use of cotton swabs dipped in water can alleviate thirst and distress; however, the effect is not ideal. Because the lips are not protected by the stratum corneum, moisturizing cotton swabs can dry the oral lip surface and even cause peeling. Therefore, the long-term thirst cannot be resolved by this method[23]. This study has been adopted the ERAS-based EBC plus ice stimulation therapy for the research group, which effectively alleviated the thirst degree and distress compared with routine care used for the control group after nursing, and indicates that the ice water spray used in this combination therapy can moisten the entire mouth by reaching the patient's throat. Ma *et al* [11] reported that ice water spray was more effective as a topical intervention for moistening the lips than a cotton swab dipped in water. Ice water spray can transform liquid into a fine water mist that quickly and evenly covers all mouth

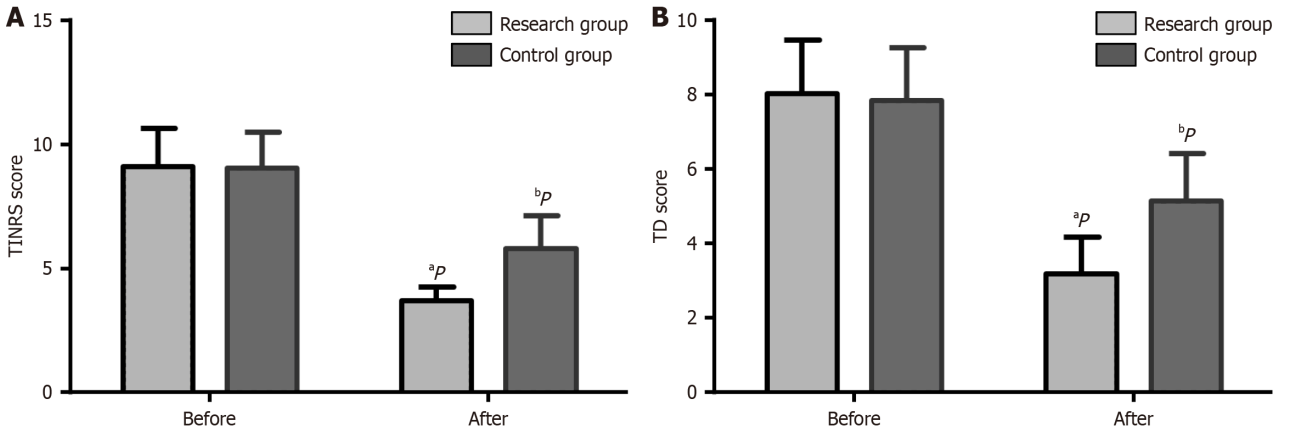

Figure 1 Evaluation of thirst intensity numerical rating scale and thirst distress scores before and after care in both groups. A: The thirst intensity numerical rating scale (TINRS) scores of both groups were markedly reduced following the nursing intervention, and the TINRS score of the research group was significantly lower than that of the control group after the nursing care; B: The thirst distress (TD) scores of both groups also manifested a significant reduction following the nursing procedures, and likewise, the TINRS score of the research group was considerably lower than that of the control group in the post-nursing phase. The TINRS scale is employed to evaluate the level of thirst, while the TD scale is utilized to assess the degree of distress induced by thirst. The scoring range for both scales spans from 0 to 10, with a higher score indicating a more severe degree of thirst or a more intense sense of distress due to thirst. $^{a}P < 0.01$ *vs* before care; $^{b}P < 0.05$ *vs* control. TD: Thirst distress; TINRS: Thirst intensity numerical rating scale.

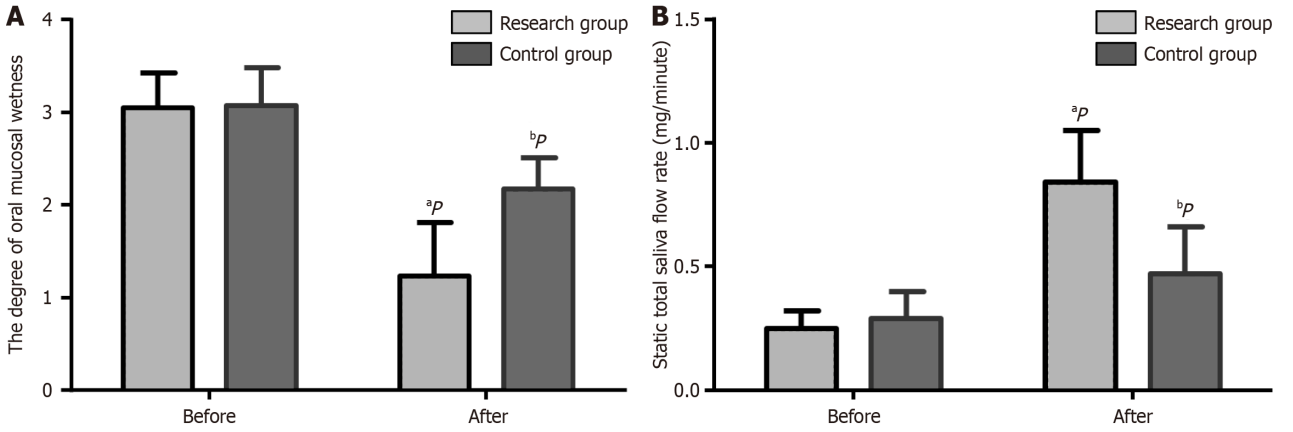

Figure 2 Evaluation of the oral mucosal wetness scores and the unstimulated whole salivary flow rate before and after nursing. A: The oral mucosal wetness scores. The oral mucosal wetness score of both groups was statistically decreased after the execution of the nursing measures, with that of the research group being significantly lower compared to the control group after nursing care. The scoring range of oral mucosal wetness degree is from 1 to 4, with a higher score signifying a reduced level of oral mucosal wetness; B: The unstimulated whole salivary flow rate. The unstimulated whole salivary flow rate of both groups was significantly increased after nursing, with a more significant increase in the research group *vs* the control group. The unstimulated whole salivary flow rate was measured by the cotton swab method. $^{a}P < 0.01$ *vs* before care; $^{b}P < 0.05$ *vs* control.

corners through the nozzle. The mist forms a protective film that, apart from effectively moisturizing the oral mucosa, reduces the dry peeling of the lips and stimulates the throat to produce more saliva, further alleviating xerostomia symptoms and thirst. Reportedly, providing ice water stimulation interventions to adult patients with postoperative thirst can effectively alleviate the moistness of the oral mucosa and be instrumental in relieving thirst[24]. This might partially explain the efficacy of nursing interventions plus ice stimulation therapy in reducing postoperative thirst following digestive surgery under general anesthesia. Next, compared with the control group, the degree of the oral mucosal wetness after nursing was significantly lower in the research group, indicating that ERAS-based EBC plus ice stimulation therapy can ensure a significant moisturizing effect on the patient's oral cavity by effectively moisturizing the entire oral mucosa and forming a protective film on its surface. Moreover, the UWSFR was higher in the research group after nursing than the control group, indicating that the ERAS-based EBC plus ice stimulation therapy effectively promotes salivary gland secretion and significantly improves the UWSFR in the oral cavity. This reduces the dryness of the patients' mouth and effectively alleviates thirst symptoms. Further, this favorably enhances the patients' oral health and digestive function, which can be attributed to the UWSFR augmentation that serves to diminishes the risk of oral infections. The enhanced saliva can effectively fulfill the cleansing functions and safeguarding of the oral cavity. Moreover, it enhances food digestion and facilitates the digestive process[25,26]. This also corroborates with Tsai *et al*'s findings, stating that oral stimulation with ice cubes or ice products can effectively relieve postoperative thirst[27]. In addition, this study demonstrated an evidently lower incidence of adverse reactions in the research group than in the

control group, indicating that the ERAS-based EBC plus ice stimulation therapy can reduce the incidence of adverse reactions caused by thirst following digestive surgery. In addition, the application of ice-cold water spray in accordance with the symptom management mode for patients admitted to ICUs effectively alleviates postoperative thirst intensity, improves oral comfort, shortens nursing time, and improves patients' satisfaction with nursing[28]. Herein, the research group expressed significantly higher overall nursing satisfaction compared with the control group, indicating that ERAS-based EBC plus ice stimulation therapy can effectively alleviate postoperative thirst and discomfort, maintain oral comfort and psychological satisfaction, and contribute to the emotional stability and physical and mental pleasure of patients, creating a positive impression regarding the nursing work.

CONCLUSION

The ERAS-based EBC plus ice stimulation therapy can effectively alleviate thirst in convalescent patients following digestive surgery under general anesthesia, thereby alleviating xerostomia symptoms, reducing adverse reactions, and enhancing patient satisfaction.

FOOTNOTES

Author contributions: Chen L designed the research and wrote the first manuscript; Chen L, Li BX and Gan QZ contributed to conceiving the research and analyzing data; Li Chen, Guo RG, Chen X and Shen X conducted the analysis; Li Chen and Chen Y provided guidance for the research; all authors reviewed and approved the final manuscript.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy of combined psychological and physical nursing in preventing peripherally inserted central catheter-related thrombosis in gastric cancer patients

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Abstract

BACKGROUND

Long-term chemotherapy for patients with gastric cancer (GC), facilitated by peripherally inserted central catheter (PICC) catheterization, reduces vascular damage and enhances drug delivery efficiency but carries risks of catheter-related complications. A combination of group psychological nursing and physical movement care significantly mitigates the risk of venous thrombosis and improves psychological well-being, and enhances motor function, underscoring its clinical importance.

AIM

To assess group psychological and physical movement nursing in preventing venous thrombosis in patients with PICC GC.

METHODS

Sixty-five GC patients with PICC, admitted from January 2022 to January 2023, were randomly divided into two groups using the lottery method: A control group (n = 35, routine nursing) and an observation group (n = 30, routine nursing plus psychological nursing and physical movement nursing). Both groups received continuous care for 2 weeks. Pre-nursing and post-nursing data on psychological state, physical function, chemotherapy-related thrombosis incidence, and cancer-related fatigue were analyzed using SPSS 26.0 and GraphPad Prism 8.0.

RESULTS

After nursing, both groups showed reduced Hamilton Anxiety Scale scores and increased General Perceived Self-Efficacy Scale scores, with the observation group performing better (P < 0.05). The Functional Comprehensive Assessment score for

the observation group after nursing was (65.42 ± 2.35) points, lower than the control group's (62.19 ± 4.33) points (P < 0.05). Although no significant difference was observed in the incidence of venous thrombosis between the two groups (χ^2 = 0.815, P = 0.367), the observation group had lower incidence. Both groups showed decreased Revised Piper Fatigue Scale scores, with the observation group scoring lower (P < 0.05).

CONCLUSION

Group psychological and physical movement nursing for patients with PICC reduces venous thrombosis risk, improves psychological well-being, cancer-related fatigue, and physical function, making it highly promotable.

Key Words: Group psychological nursing; Physical movement nursing; Peripherally inserted central catheter; Gastric cancer; Venous thrombosis; Cancer-related fatigue

Core Tip: In a comprehensive care approach that integrates psychological counseling with physical activity, there is a significant reduction in the risk of thrombosis among gastric cancer patients, particularly those who have undergone percutaneous central venous catheterization. This strategy not only enhances the overall health status of patients but also specifically targets individuals requiring long-term venous therapy due to gastric cancer, offering an effective method for thromboprophylaxis.

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INTRODUCTION

Gastric cancer (GC), one of the most common malignant tumors, requires prolonged chemotherapy. Repeated vascular punctures increase the risk of vascular damage and complications such as subcutaneous tissue necrosis due to drug extravasation[1]. In recent years, with the continuous promotion of peripherally inserted central catheter (PICC) catheterization, advantages such as protecting blood vessels, rapidly delivering drugs to central veins, and accelerating drug distribution have led to significant therapeutic effects in clinical practice[2]. However, complications such as catheter dislodgement, phlebitis, and venous thrombosis are inevitable during the catheterization process and can affect subsequent treatments. Therefore, exploring measures to reduce venous thrombosis risk in GC patients with PICC is a key focus of clinical research[3,4]. Physical movement can effectively promote local blood circulation in patients with tumors and help prevent thrombosis. However, the psychological state of several patients with GC, affected by fear of cancer and a lack of confidence in treatment, can affect the effectiveness of daily treatment. Compared to routine nursing, group psychological nursing is a novel intervention strategy guided by a psychologist and carried out by a professional team through systematic observation, expression, and communication. This approach aims to transform patients' cognitive structures and effectively alleviate or eliminate negative emotions. It emphasizes teamwork and professional guidance to achieve positive effects on the patients' psychological well-being. Currently, there is limited research on combining group psychological nursing with physical movement nursing for GC patients with PICC. This study observed 65 GC patients with PICC admitted to our hospital and analyzed the application value of this combined nursing approach.

MATERIALS AND METHODS

General data

Sixty-five patients with PICC, admitted between January 2022 and January 2023, were selected. Diagnostic criteria were in accordance with "The Chinese Society of Clinical Oncology: Clinical guidelines for the diagnosis and treatment of GC, 2021"[3]. The inclusion criteria were as follows: (1) Meeting the aforementioned diagnostic criteria and undergoing PICC treatment; (2) Concurrent vitamin K deficiency; (3) No mental disorder; (4) Suitable vessels for puncture; and (5) Informed consent obtained from patients and family members. The exclusion criteria included: (1) Poor compliance; (2) Cellulitis; (3) Active infection at the catheter site; (4) Communication or hearing impairment; and (5) Coagulation mechanism disorders. Patients were randomly divided into two groups using the ball-drawing method: A control group (n = 35) and an observation group (n = 30), with no significant difference in general data between the two groups (P > 0.05) (Table 1).

Table 1 Comparison of general information of two groups of patients

General information	Observation (n = 30)	Control (n = 35)	$F/t/\chi^2$	P value
Average age (years), mean ± SD	52.33 ± 5.84	53.18 ± 6.42	0.559	0.578
Gender (n)				
Male	19	20	0.258	0.612
Female	11	15	-	-
Catheter vein (n)				
Median cubital vein	11	13	0.511	0.775
Subclavian vein	10	14	-	-
Venae magnalis	9	8	-	-
Average BMI (kg/m^2), mean ± SD	21.11 ± 3.11	22.02 ± 3.12	1.174	0.245
TNM staging				
T1 stage	15	20	1.389	0.499
T2 stage	6	5		
T3 stage	9	6		

BMI: Body mass index; TNM: Tumor-node-metastasis.

Methods

Control group (standard care): During the treatment period, nursing staff were required to assess various vital signs of the patients, including their heart rate and blood pressure. They provided guidance on a scientific diet, avoided cold and greasy foods, and emphasized the safety of catheter placement.

Observation group: In addition to the standard care provided to the control group, the observation group received an integrated program of psychological and physical movement nursing: (1) Formation of the integrated nursing team: The team consisted of one psychological physician, one attending oncology physician, one head nurse, and several nursing staff members. Prior to the study, team members underwent training and assessment on the content of group psychological and physical movement nursing; (2) Psychological intervention: The psychological physician and nursing staff developed intervention content tailored to the actual situation of patients with GC with PICC. Preparation activity: Before the start of group psychological nursing, the physician conducted one-on-one conversations with patients to build rapport and foster confidence in treatment. The WeChat group was established by the nursing staff prior to the first group's psychological activity. Getting to know each other activity: This activity aimed to clarify intervention goals and facilitate familiarity among team members through self-introductions. The physician initiated the process, helping each member define their expected goals and outcomes, encouraging patients to share their situations and concerns, and providing a summary. Emotional expression activity: Starting with the physician, each participant described themselves with an adjective, and subsequent participants built on the previous introduction until all members had introduced themselves. The physician explained the rules, played relevant songs to enliven the atmosphere, and the members expressed emotions such as happiness or sadness until everyone had finished, marking the end of one round. After the two rounds, the members reflected on their experiences. Self-understanding activity: Patients were guided to create self-portraits and share the meanings of different elements within them. The nursing staff prepared cards for patients to record their self-awareness and hopes for their future progress. All cards were collected and placed in a box from which the patients drew cards and read the content aloud, offering support and encouragement to the card owner. Facing life activity: The physician instructed patients to draw a coordinate axis on A4 paper, with the horizontal axis representing age from birth to the present and the vertical axis representing life satisfaction. The patients were guided to recall and mark significant turning points and trends in satisfaction changes by sharing these points with the group. The physician provided targeted advice based on shared experiences, highlighting potential future challenges. Messages for the future activity: Group members wrote down reflections on "progress made", "happiest moments", "greatest help received", and "future expectations", and composed messages for peers, summarizing their gains and feedback on goal achievement. Implementation frequency: Each session lasts for 1.5 hours and was conducted once every 2 weeks; and (3) Physical movement nursing: This included finger flexion and extension, first clenching, and wrist rotation. Patients were instructed to flex and extend their fingers 25 times per set, rest for 10-15 seconds, and then grip a stress ball forcefully for 15 seconds, with a 5-second rest per set. The training session lasted for 15 minutes, 2-3 times a day. Nursing staff also instructed the patients to clench their fists with palms facing outward, extend laterally, and then rotate internally for 1 minute each. These exercises were done for 10-15 minutes per session, 2-3 times daily.

Observational indicators

Psychological state: The psychological state was assessed before and after nursing using the Hamilton Anxiety Scale (HAMA) and General Perceived Self-Efficacy Scale (GSES). The HAMA uses a 0-4 scoring system, with higher scores indicating more severe anxiety symptoms. The GSES consists of 10 items measuring self-confidence in overcoming difficulties or setbacks, scored from 1 to 4. Higher total scores indicate stronger self-efficacy.

Physical movement function: Functional comprehensive assessment (FCA) was used to assess physical movement function before and after nursing. The FCA includes two dimensions, physical and cognitive function, with a total score of 108. Higher scores indicate stronger overall physical function.

Thrombosis incidence during chemotherapy: The incidence of venous thrombosis during chemotherapy was recorded for both groups of patients.

Cancer-related fatigue: The Revised Piper Fatigue Scale (PFE-R) was used to evaluate cancer-related fatigue, with 22 items and five open-ended questions scored 0-10, with higher scores indicating more severe fatigue.

Statistical analysis

All data collected in this study were statistically analyzed using SPSS 26.0. Quantitative data are described as mean ± SD, with inter-group comparisons made using independent samples *t*-tests and intra-group comparisons made using paired samples *t*-tests. Count data are presented as percentages and compared using χ^2 tests, with $P < 0.05$ indicating significant differences.

RESULTS

Psychological state

Following the nursing intervention, there was a decrease in HAMA scores and an increase in GSES scores in the patients, with the intervention group showing superior psychological state scores compared to the control group ($P < 0.05$), as shown in Table 2.

Motor function

Post-nursing care, both groups exhibited an increase in FCA scores, with the intervention group demonstrating higher scores ($P < 0.05$), as detailed in Table 3.

Thrombosis incidence during chemotherapy

The incidence of thrombosis was 6.67% (2/30) and 17.14% (6/35) in the intervention and control groups, respectively. There was no significant difference in thrombosis incidence between the two groups ($\chi^2 = 0.815$, $P = 0.367$), although the intervention group had a lower incidence.

Cancer-related fatigue

After the nursing intervention, there was a decrease in all PFE-R scores in both groups, with the intervention group showing significantly lower PFE-R scores ($P < 0.05$), as presented in Table 4.

DISCUSSION

The PICC is a relatively safe vascular access device typically used for patients requiring prolonged intravenous infusions or frequent venipuncture for therapy[5,6]. Patients with GC who undergo long-term chemotherapy often present with poor vascular conditions, where repeated punctures can lead to drug extravasation. This not only compromises treatment efficacy but also exacerbates vascular strain[7]. Consequently, effective catheter care interventions are essential to prevent PICC-related venous thrombosis[8]. Studies have suggested that patients with cancer, driven by the fear of the disease, weak confidence in treatment, and concerns about treatment costs, often experience heightened levels of anxiety, depression, and other negative emotions[9]. Although psychological interventions in routine nursing can effectively alleviate symptoms, their ability to significantly improve patients' psychological state is limited due to patients' misconceptions about GC and low trust in treatment methods[10]. Group psychological nursing, as a form of collective intervention, helps address individual and shared issues by leveraging team building, enhanced communication, and emotional support for patients[11]. Additionally, physical movement nursing can promote local blood circulation and dilate local venous vessels through physical activity, contributing to improved vascular.

After nursing, both groups showed a decrease in HAMA scores and an increase in GSES scores, with the observation group's psychological state scores being significantly better than those of the control group ($P < 0.05$). The analysis indicated that group nursing interventions, through collective activities, can reduce patients' feelings of loneliness and anxiety by providing a sense of support and belonging. A psychologist's targeted guidance can help patients develop a positive and proactive mindset[12]. During physical movement nursing, patients can promote blood circulation, prevent thrombosis through physical activities, and master the methods of activity training, thereby building confidence in their

Table 2 Pre-nursing and post-nursing psychological state score comparison between two groups

Groups	Cases	HAMA (scores)		*t*	*P* value	GSES (scores)		*t*	*P* value
		Before	After			Before	After		
Observation, mean ± SD	30	36.44 ± 3.42	20.53 ± 1.84	22.439	< 0.001	28.75 ± 4.12	36.58 ± 6.22	5.748	< 0.001
Control, mean ± SD	35	36.39 ± 3.30	21.61 ± 2.13	22.262	< 0.001	28.75 ± 4.22	31.25 ± 4.78	2.320	< 0.001
t	-	0.060	2.168	-	-	0.000	3.902	-	-
P value	-	0.952	0.034	-	-	1.000	< 0.001	-	-

HAMA: Hamilton Anxiety Scale; GSES: General Perceived Self-Efficacy Scale.

Table 3 Pre-nursing and post-nursing physical movement function score comparison between two groups

Groups	Cases	FCA score		*t*	*P* value
		Before	After		
Observation, mean ± SD	30	40.46 ± 6.58	65.42 ± 2.35	19.566	< 0.001
Control, mean ± SD	35	40.21 ± 6.13	62.19 ± 4.33	17.326	< 0.001
t	-	0.158	3.648	-	-
P	-	0.875	0.001	-	-

FCA: Functional comprehensive assessment.

Table 4 Pre-nursing and post-nursing cancer-related fatigue score comparison between two groups

Items	Time	Observation (*n* = 30)	Control (*n* = 35)	*t*	*P* value
Emotion (scores), mean ± SD	Before	7.33 ± 1.12	7.22 ± 1.18	0.384	0.703
	After	2.41 ± 0.64	4.56 ± 0.77	12.118	< 0.001
t	-	20.891	11.169	-	-
P value	-	< 0.001	< 0.001	-	-
Cognition (points)	Before	6.68 ± 1.44	6.71 ± 1.51	0.082	0.935
	After	1.87 ± 0.44	2.64 ± 0.74	4.990	< 0.001
t'	-	17.497	14.319	-	-
P value	-	< 0.001	< 0.001	-	-
Behavior (points)	Before	8.44 ± 1.51	8.51 ± 1.46	0.190	0.850
	After	2.02 ± 0.43	3.02 ± 0.65	7.183	< 0.001
t'	-	22.397	20.323	-	-
P value	-	< 0.001	< 0.001	-	-
Body (points)	Before	7.46 ± 1.13	7.33 ± 1.24	0.439	0.662
	After	2.03 ± 0.41	2.45 ± 0.55	3.441	0.001
t'	-	24.742	21.283	-	-
P value	-	< 0.001	< 0.001	-	-

treatment. One study reported that after the intervention, the incidence of mechanical phlebitis, infection, catheter obstruction, and venous thrombosis in the observation group was lower than in the control group ($P < 0.05$). This indicates that group psychological nursing not only improves patients' psychological state but also reduces the occurrence of complications[13]. These findings align with our results, demonstrating that physical movement nursing promotes blood circulation, prevents thrombosis, and helps patients build confidence in treatment[14].

Furthermore, post-nursing, the observation group's PFE-R scores were lower than those of the control group ($P < 0.05$). The analysis showed that compared with routine nursing, the combination of group psychological nursing and physical movement nursing can effectively alleviate cancer-related fatigue in patients. This was attributed to the group's psychological nursing ability to enhance patients' self-awareness and self-acceptance, thereby improving their emotional control capabilities. Physical movement nursing helps patients move their limb extremities, promotes peripheral nerves, and improves blood circulation through activities such as fist clenching and finger flexion. The combined nursing approach enabled patients to correctly understand PICC-related venous thrombosis in GC and chemotherapy, thereby alleviating the psychological fatigue caused by cancer[15]. One study investigated the application of psychological nursing combined with exercise therapy in diabetes care and analyzed its impact on the quality of life. The results demonstrated that compared with routine nursing, the integration of psychological nursing and exercise therapy significantly improved patients' glycemic control and quality of life ($P < 0.05$). This finding is congruent with our observation that physical movement nursing can promote blood circulation, prevent thrombosis, and bolster patient confidence in treatment[16].

The comparison of thrombosis incidence between the two groups showed no statistically significant difference ($\chi^2 = 0.815$, $P = 0.367$), but the incidence was lower in the observation group. The analysis revealed that during physical movement nursing, guidance from nursing staff on exercises, such as slow finger flexion and extension, first clenching, and wrist rotation, aims to improve peripheral blood circulation and promote local blood flow recovery. This enhances vascular strength and reduces the incidence of local venous thrombosis. Concurrently, the combination of group psychological nursing allowed patients to engage in local physical activities during the group activities, further promoting blood circulation improvement[17]. A study found that combining ankle pump exercises with intermittent pneumatic compression therapy significantly reduced the incidence of lower extremity deep vein thrombosis, with a statistically significant difference ($P < 0.05$)[18]. This finding suggests that limb movement nursing plays a beneficial role in decreasing the occurrence of venous thrombosis, consistent with our findings that physical movement nursing can promote blood circulation, prevent thrombosis, and foster patients' confidence in their treatment. However, this study was hospital-based, potentially introducing selection bias and limiting the representativeness of the sample for the general population. Future validation will involve a larger and more diverse sample to address these limitations and expand the generalizability of the findings.

CONCLUSION

In conclusion, this pioneering study integrated group psychological nursing with physical movement care for patients with GC undergoing PICC therapy. Our findings revealed that this novel, comprehensive nursing approach significantly reduced the risk of venous thrombosis, markedly ameliorated cancer-related fatigue, and enhanced the patients' motor function. These results introduce an innovative strategy for the clinical care of patients with GC and hold significant implications for guiding clinical practice, advocating for the broader adoption of this nursing model in clinical settings.

FOOTNOTES

Author contributions: Ni WJ designed the research study; Ni WJ and Xi YX contributed new reagents and analytical tools; Xi YX and Zhou YC jointly designed the research, performed the research super, wrote the manuscript, vised the entire process, interpreted the results, and were responsible for manuscript revision and communication with the journal, ensuring the integrity and quality of the study, they contributed equally to this article, they are the co-corresponding authors of this manuscript; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Effect of forearm and posterior wall anastomosis on gastroesophageal reflux in proximal gastrectomy patients

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Abstract

BACKGROUND

Proximal gastrectomy for gastric cancer often leads to postoperative gastroesophageal reflux (GER). This study compares the impact of forearm anastomosis and posterior wall anastomosis techniques on GER in patients undergoing this procedure.

AIM

To identify the most effective method for reducing reflux symptoms while preserving gastrointestinal integrity and nutritional status.

METHODS

A retrospective evaluation was conducted on 60 patients who underwent proximal gastrectomy between December 2020 and December 2023, divided equally into two groups based on the anastomosis technique used (forearm or posterior wall). GER symptoms were assessed using the GER disease questionnaire (GerdQ) preoperatively and on the first postoperative day. Biochemical markers [diamine oxidase (DAO), D-lactic acid, and endotoxin (ETX)] and nutritional indicators [serum ferritin (SF), prealbumin (PA), and albumin (ALB)] were measured to evaluate gastrointestinal barrier function and nutritional status.

RESULTS

Both groups showed significant improvements in GerdQ scores and reflux symptom scores post-treatment, with the observation group exhibiting greater reductions. Biochemical markers indicated enhanced gastrointestinal barrier function post-treatment in both groups, with notable increases in DAO, D-lactic, and ETX levels. Nutritional status indicators also demonstrated significant changes, with reductions in SF, PA, and ALB levels, suggesting an impact of treatment on inflammatory and nutritional status.

CONCLUSION
The forearm anastomosis technique appears to be more effective in reducing GER symptoms and preserving gastrointestinal health in patients undergoing proximal gastrectomy for gastric cancer compared to the posterior wall anastomosis technique. These preliminary findings advocate for further research to confirm the benefits and potentially standardize Forearm Anastomosis in surgical practice for gastric cancer.

Key Words: Proximal gastrectomy; Gastroesophageal reflux; Forearm anastomosis; Posterior wall anastomosis; Gastric cancer

Core Tip: This manuscript provides a comprehensive analysis of two distinct anastomosis techniques and their effects on postoperative gastroesophageal reflux (GER), an issue of paramount importance in the surgical management of gastric cancer. Our study embarked on a meticulous comparative evaluation between forearm anastomosis and posterior wall anastomosis techniques, focusing on their efficacy in mitigating GER symptoms and their impact on the gastrointestinal barrier function and nutritional status of the patient's post-proximal gastrectomy. Through rigorous assessment and detailed analysis, our findings illuminate the superior benefits of the Forearm Anastomosis technique, not only in reducing GER symptoms but also in preserving gastrointestinal health.

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INTRODUCTION

Proximal gastric cancer, a subtype affecting the upper portion of the stomach and the gastroesophageal junction, necessitates a specialized surgical approach known as proximal gastrectomy[1]. Unlike total gastrectomy, which involves the complete removal of the stomach, or distal gastrectomy, which involves the removal of the lower portion of the stomach, proximal gastrectomy specifically targets the upper segment of the stomach, preserving much of the gastric body and pylorus. This approach is aimed at maintaining gastrointestinal function, particularly preserving the patient's nutritional status and digestive capacity, while ensuring adequate oncological resection of the cancerous tissue[2,3]. The primary challenge in proximal gastrectomy lies in balancing oncological safety with the preservation of stomach function, which is a critical factor in determining postoperative quality of life.

The postoperative phase following proximal gastrectomy, however, is frequently overshadowed by a spectrum of complications, among which gastroesophageal reflux (GER) disease (GERD) emerges as particularly prevalent and debilitating. GERD, characterized by the retrograde flow of gastric contents into the esophagus, manifests through symptoms such as heartburn, regurgitation, and potential esophageal mucosal damage[4,5]. The incidence of GERD after proximal gastrectomy has been reported to range from 20% to 60%, with some studies suggesting that nearly half of patients experience moderate to severe symptoms postoperatively[6]. The pathophysiology of GERD post-gastrectomy is multifaceted, with the surgical reconstruction of the digestive tract playing a central role in the development and severity of reflux symptoms. Traditional reconstruction techniques, while effective in re-establishing gastrointestinal continuity, often fall short in preventing the backflow of acidic gastric contents into the esophagus, leading to a high incidence of GERD.

In light of the constraints of traditional reconstructive approaches, there is increasing interest in investigating alternate anastomosis techniques designed to diminish the occurrence of postoperative GERD. The forearm anastomosis and posterior wall anastomosis procedures have attracted interest for their novel methodology in gastroesophageal junction restoration. The forearm anastomosis procedure entails constructing a conduit from the vascularized tissue of the forearm, subsequently anastomosed to the residual stomach and esophagus. This approach is posited to offer a more natural angle and resistance to the retrograde passage of stomach contents[7]. The posterior wall anastomosis approach entails the direct connection of the posterior wall of the residual stomach to the esophagus, which may diminish stress at the anastomotic site and hence lower the risk of reflux[8]. In comparison to traditional anastomosis techniques, both the forearm anastomosis and posterior wall anastomosis techniques have demonstrated promising efficacy in reducing the incidence and severity of postoperative GER, as reported in previous studies[9-11]. The primary objective of this research is to evaluate the impact of these two anastomosis techniques on both the incidence and severity of GER (GERD), as well as postoperative quality of life in patients undergoing proximal gastrectomy for gastric cancer. By comparing the outcomes associated with the forearm and posterior wall anastomosis techniques, this study aims to identify the more effective surgical approach in reducing GERD symptoms while simultaneously preserving gastrointestinal integrity and improving overall postoperative well-being.

MATERIALS AND METHODS

Study design

A comprehensive retrospective analysis was performed at our hospital to evaluate the effectiveness of the forearm anastomosis technique and its influence on GER following curative proximal gastrectomy for gastric cancer. This study extended from December 2020 to December 2023, concentrating on a group of 30 patients who received digestive tract restoration utilizing the forearm anastomosis method. The people were assigned as the case group for comprehensive analysis. A control group was created for a thorough comparison, consisting of 30 patients who received the posterior wall anastomosis procedure over the same period. This method established a baseline comparability between the two groups, facilitating a nuanced comprehension of the varying effects of these anastomosis procedures on postoperative outcomes, particularly GER. Informed consent was secured from all study participants, highlighting the voluntary aspect of their involvement and the clear disclosure of the study's aims and methods. The research technique, encompassing the study's objectives and methods, was rigorously evaluated by the ethical committee of our institution.

Inclusion and exclusion criteria

Eligible participants for this study were individuals aged 18 years and older, diagnosed with proximal gastric cancer *via* histopathological examination, who underwent curative proximal gastrectomy utilizing either forearm anastomosis or posterior wall anastomosis techniques between December 2020 and December 2023. All participants were mandated to submit written informed consent, confirming their comprehension and willing involvement in the study.

The study excluded patients having a history of prior gastric surgery due to its potential impact on the outcomes of proximal gastrectomy and anastomosis procedures. Individuals with metastatic illness or stomach cancer unsuitable for curative resection were also excluded. Individuals with significant concurrent medical issues that made them unfit for surgery, including advanced heart illness, uncontrolled diabetes, or severe chronic obstructive pulmonary disease, were likewise eliminated. Additionally, patients who underwent chemotherapy or radiotherapy for stomach cancer before to the operation were excluded to guarantee the integrity of the evaluation of the anastomosis techniques' efficacy.

Surgical techniques

The forearm anastomosis technique was employed for digestive tract restoration in the observation group after radical proximal gastrectomy. The stomach remnant was turned 45 degrees to the right, enabling the insertion of a trocar through a predetermined hole. The trocar's needle was precisely positioned to penetrate the front wall of the gastric remnant, 5 cm from the cut edge, ensuring correct alignment with the reserved esophageal stump for a successful single fire. A gastric tube was subsequently placed *via* the pylorus into the duodenum. The jejunum was located 30 cm distal to the Treitz ligament and sealed with a 45-mm disposable intraluminal stapler, maintaining an aperture for later manual suturing around the esophagus, gastrointestinal mucosa, and anastomosis site to guarantee closure. The stomach's curvature was secured next to the left diaphragmatic crura, forming an artificial gastric fundus. Hemostasis was carefully attained, succeeded by a sterile saline irrigation of the peritoneal cavity. A rubber drainage tube was positioned at the anastomosis site, extending through Winslow's foramen and along the right colic gutter, conforming to the downward trajectory of the right puncture site. The abdominal cavity was then closed in layers.

The posterior wall anastomosis procedure was utilized in the control group. Like the observation group, this entailed a major proximal gastrectomy, succeeded by the direct placement of a trocar *via* the designated opening. The needle was calibrated to penetrate the posterior wall, 5 cm from the resection edge of the stomach remnant. The following procedures, such as the insertion of the gastric tube, formation of an artificial gastric fundus, and drainage, were similar to those executed in the observation group, maintaining procedural uniformity and comparability between the two groups.

Data collection and evaluation criteria

This study employed a comprehensive set of observational indicators and evaluation criteria to assess the outcomes and impact of forearm anastomosis and posterior wall anastomosis techniques on GER symptoms in patients undergoing proximal gastrectomy for gastric cancer.

GER symptom assessment: GER symptoms in both cohorts were assessed preoperatively and on the first postoperative day utilizing the GERD questionnaire (GerdQ). The GerdQ comprises six items, each rated from 0 to 3, resulting in a possible total score of 18. Elevated scores signify increased symptom severity. Simultaneously, a bespoke scale created by our institution, encompassing dimensions of regurgitation, retrosternal pain, belching, and heartburn, was employed. Each dimension was classified as severe (6 points), moderate (4 points), mild (2 points), or none (0 points), with the scale exhibiting a reliability coefficient of 0.801, signifying strong dependability.

Biochemical markers: Venous blood samples (5 mL) were obtained from the upper limbs of patients in both groups before to surgery and on the first postoperative day. The samples underwent centrifugation at 3000 rpm for 10 minutes, and the resultant supernatant serum was utilized for analysis. Diamine oxidase (DAO) and D-lactic acid levels were determined by a colorimetric test kit, whilst endotoxin (ETX) levels were assessed using the limulus amebocyte lysate chromogenic substrate method. The test kits were obtained from Shanghai Yu Bo Biotech Co., Ltd., and all protocols were meticulously followed in accordance with the manufacturer's guidelines.

Serum protein levels and nutritional status: Preoperative and postoperative day one fasting venous blood samples (5 mL) were obtained from patients, centrifuged at 3000 rpm for 10 minutes, and the serum was preserved at -70 °C for

subsequent analysis. Serum ferritin (SF) levels were assessed utilizing a BS-820 automatic biochemical analyzer employing the ferrozine method. Prealbumin (PA) concentrations were quantified *via* turbidimetry, while albumin (ALB) concentrations were evaluated using the bromocresol green method. The assay kits were obtained from Shanghai Jing Kang Bio-Tech Co., Ltd., and tests were conducted in accordance with the kit instructions. Additionally, patients' weight and height were measured to calculate the body mass index (BMI) using the formula: BMI = weight (kg)/height^2 (m^2).

Statistical analysis

Statistical analyses in this study were performed using SPSS (Version 27.0), starting with the categorization of data into quantitative and categorical groups, and subsequently conducting normality checks to determine distribution patterns. Group differences in normally distributed quantitative data were assessed using independent *t*-tests, with findings reported as means and standard deviations. Quantitative data that were not normally distributed were evaluated using the Mann-Whitney *U* test, with medians and interquartile ranges [M (P25, P75)] given. Categorical data were evaluated with χ^2 testing, reported as frequencies and percentages. Significance was evaluated at a P value < 0.05, ensuring stringent hypothesis testing.

RESULTS

Participant analysis

The control group consisted of 18 male and 12 female patients, aged between 25 and 68 years (mean age: 50.12 ± 5.16 years). The tumor diameters ranged from 1.1 to 4.2 cm, with a mean diameter of 3.16 ± 0.38 cm. The BMI ranged from 20.3 to 25.6 kg/m^2, with a mean of 23.12 ± 1.38 kg/m^2. The TNM staging distribution comprised 16 cases at stage IA, 8 instances at stage IB, and 6 cases at stage IIA. The observation group comprised 17 male and 13 female patients, aged 26 to 67 years (mean age: 49.16 ± 6.58 years). Tumor sizes varied from 1.2 to 4.1 cm, with a mean of 2.91 ± 0.35 cm. The BMI readings ranged from 20.6 to 25.8 kg/m^2, with a mean of 23.16 ± 1.26 kg/m^2. In terms of TNM staging, there were 17 instances classified as stage IA, 7 cases as stage IB, and 6 cases as stage IIA. Statistical analysis indicated no significant variations in the demographic and clinical characteristics between the two groups (P > 0.05), demonstrating homogeneity in the baseline data and confirming the comparability of post-treatment results between the observation and control groups.

Comparative evaluation of GerdQ scores and reflux symptom scores pre- and post-treatment in observation and control groups

The study results highlight substantial enhancements in GERD symptoms and GerdQ scores following therapy in both the observation and control groups, as demonstrated by the statistical analyses. Both groups showed significant reductions in GerdQ scores and reflux symptom scores post-treatment; however, the observation group shown a more substantial improvement than the control group. Following therapy, the observation group exhibited a dramatic reduction in GerdQ scores, with mean scores declining from 14.66 to 7.32, indicating a significant amelioration of GERD symptoms. The control group experienced an improvement as well, with GerdQ values decreasing from 14.62 to 10.35, though at a lower degree than the observation group. The disparity in post-treatment GerdQ ratings between the two groups was statistically significant, underscoring the enhanced efficacy of the treatment method employed in the observation group. The examination of certain reflux symptoms, such as regurgitation, retrosternal discomfort, and belching, demonstrated notable post-treatment enhancements in each cohort. The observation group exhibited a significant decrease in symptom severity, with post-treatment scores reflecting a low presence of symptoms. Conversely, although the control group exhibited improvements in these symptoms, the degree of reduction was less significant than that of the observation group. The statistical analysis of pre- and post-treatment scores within each group shown substantial differences, highlighting the therapies' efficacy in alleviating GERD symptoms. Inter-group comparisons underscored the superior outcomes in the observation group, exhibiting reduced post-treatment scores for all assessed symptoms relative to the control group (Table 1).

Comparative analysis of gastrointestinal barrier function markers before and after treatment

The research evaluated the impact of gastrointestinal therapies on biomarkers reflecting intestinal health and microbial equilibrium, specifically DAO, D-lactic Acid, and ETX, in both the observation and control cohorts. Post-treatment assessments indicated substantial increases in all evaluated biomarkers, underscoring the physiological effects of the therapeutic measures. In the observation group, DAO levels rose from 1.53 IU/L to 2.25 IU/L, while the control group exhibited a comparable increase, with levels escalating from 1.56 IU/L to 3.18 IU/L, signifying improved enzymatic activity associated with intestinal mucosal integrity following treatment. D-lactic acid levels, indicative of metabolic byproducts from gut microbiota, exhibited a significant rise in both groups, implying alterations in microbial metabolism. Significant changes were noted in ETX levels, which more than quadrupled after treatment in both groups, indicating modifications in gut microbial ETX levels (Table 2).

Comparative evaluation of nutritional status indicators before and after treatment

The study's results indicate substantial alterations in nutritional and inflammatory indicators, including SF, PA, and ALB, after treatment in both the observation and control groups. The pre-treatment levels of these markers were similar across

Table 1 Pre- and post-treatment gastroesophageal reflux disease questionnaire scores and reflux symptom scores in observation and control groups, mean ± SD

Measurement	Observation group	Control group	*t* value	*P* value
GerdQ score pre-treatment	14.66 ± 1.66	14.62 ± 1.71	0.08	0.95
GerdQ score post-treatment	7.32 ± 1.10[1]	10.35 ± 1.37[1]	7.191	< 0.001
Reflux symptom pre-treatment	3.27 ± 1.17	3.24 ± 1.10	0.09	0.94
Reflux symptom post-treatment	1.13 ± 0.64[1]	1.97 ± 0.90[1]	3.168	0.002
Regurgitation pre-treatment	1.97 ± 0.88	1.96 ± 0.84	0.04	0.98
Regurgitation post-treatment	0.93 ± 0.22[1]	1.42 ± 0.47[1]	3.971	< 0.001
Retrosternal pain pre-treatment	1.64 ± 0.58	1.65 ± 0.59	0.06	0.96
Retrosternal pain post-treatment	0.63 ± 0.25[1]	1.18 ± 0.34[1]	5.446	< 0.001
Belching pre-treatment	2.17 ± 0.64	2.20 ± 0.59	0.16	0.88
Belching post-treatment	0.66 ± 0.25[1]	1.40 ± 0.33[1]	8.273	< 0.001

[1]Comparisons within the same group pre- and post-treatment are marked with an asterisk, indicating a statistically significant difference with a *P* value less than 0.05.
GerdQ: Gastroesophageal reflux disease questionnaire.

Table 2 Diamine oxidase, D-lactic, and endotoxin levels pre- and post-treatment in observation and control groups

Measurement	Pre-treatment observation	Post-treatment observation	Pre-treatment control	Post-treatment control	*t* value	*P* value
DAO (IU/L)	1.53 ± 0.24	2.25 ± 0.50[1]	1.56 ± 0.28	3.18 ± 0.62[1]	5.409	< 0.01
D-lactic (mg/L)	2.78 ± 0.56	3.44 ± 0.76[1]	2.72 ± 0.54	4.29 ± 0.87[1]	3.357	< 0.01
ETX (EU/mL)	0.41 ± 0.14	1.36 ± 0.33[1]	0.39 ± 0.16	1.71 ± 0.45[1]	3.451	< 0.01

[1]Comparisons within the same group pre- and post-treatment are marked with an asterisk, indicating a statistically significant difference with a *P* value less than 0.05.
DAO: Diamine oxidase; ETX: Endotoxin.

the groups, giving a baseline for assessing the treatment's effect. Post-treatment analysis indicated a reduction in SF levels from 94.67 μg/L to 82.54 μg/L in the observation group, whereas the control group exhibited a more significant decline from 95.40 μg/L to 74.28 μg/L, suggesting a possible decrease in inflammation or iron reserves. Likewise, PA levels, reflecting nutritional status and inflammation, diminished in both cohorts during treatment, with the observation group decreasing from 254.82 mg/L to 236.44 mg/L and the control group from 255.94 mg/L to 220.18 mg/L. ALB levels, indicative of nutritional status and chronic inflammation, exhibited a notable decline, especially in the control group, where levels diminished from 39.98 g/L to 35.08 g/L following therapy. These modifications indicate an effect of the treatment on nutritional and inflammatory state, with the control group displaying more significant changes (Table 3).

DISCUSSION

Proximal gastrectomy for gastric cancer carries a significant risk of postoperative GERD, which can severely impact patient quality of life[12,13]. Various anastomosis techniques, including forearm and posterior wall anastomosis, have been explored to mitigate this complication[14,15]. The aim of this study is to compare the efficacy of these two techniques in reducing GERD symptoms, preserving gastrointestinal integrity, and improving overall postoperative well-being in patients undergoing proximal gastrectomy for gastric cancer. Through this comparison, the study seeks to identify the more effective surgical approach in minimizing reflux while optimizing long-term recovery[16,17]. This study provides novel insights into the comparative efficacy of the Forearm Anastomosis technique *vs* the posterior wall anastomosis technique in mitigating GERD symptoms following curative proximal gastrectomy for gastric cancer. The key innovation lies in its prospective analysis of gastrointestinal barrier function, microbial balance, and nutritional status using objective biomarkers such as DAO, D-lactic acid, and ETXs, alongside traditional GERD assessments. Notably, the Forearm Anastomosis technique demonstrated superior outcomes in reducing GERD symptoms, as evidenced by significant improvements in GerdQ scores and reflux symptom severity. Additionally, the study highlights the potential

Table 3 Levels of serum ferritin, prealbumin, and albumin pre- and post-treatment in observation and control groups

Measurement	Pre-treatment observation	Post-treatment observation	Pre-treatment control	Post-treatment control	*t* value	*P* value
SF (μg/L)	94.67 ± 10.90	82.54 ± 11.67[1]	95.40 ± 10.99	74.28 ± 9.66[1]	2.519	0.016
PA (mg/L)	254.82 ± 18.31	236.44 ± 17.88[1]	255.94 ± 18.33	220.18 ± 14.79[1]	3.237	< 0.01
ALB (g/L)	40.54 ± 4.40	38.73 ± 3.65	39.98 ± 3.99	35.08 ± 3.65[1]	4.173	< 0.01

[1]Comparisons within the same group pre- and post-treatment are marked with an asterisk, indicating a statistically significant difference with a *P* value less than 0.05.
SF: Serum ferritin; PA: Prealbumin; ALB: Albumin.

for both techniques to influence intestinal integrity and nutritional status, with the forearm anastomosis showing more favorable results in certain biomarkers. Clinically, these findings underscore the importance of surgical technique selection in enhancing postoperative quality of life, particularly in reducing reflux complications and improving long-term gastrointestinal health and nutritional recovery post-gastrectomy. This research contributes valuable evidence for optimizing surgical strategies in gastric cancer care.

This study's outcomes yield valuable data regarding the effects of therapeutic interventions on GERD symptoms, gastrointestinal barrier function, and nutritional status in patients receiving therapy for gastric-related diseases. The notable enhancements in GERD symptoms and GerdQ scores following therapy, especially in the observation group, highlight the effectiveness of the implemented therapeutic strategy. The significant reduction in GerdQ scores from 14.66 to 7.32 in the observation group indicates a considerable improvement in GERD symptoms, likely due to the targeted intervention techniques utilized, which may have more effectively restored gastroesophageal junction integrity and diminished acid reflux occurrences. The significant improvements in gastrointestinal barrier function markers, such as DAO, D-Lactic Acid, and ETX, following therapy in both groups, indicate a favorable transition towards enhanced intestinal health and microbial equilibrium. The increase in DAO levels following therapy suggests improved mucosal barrier integrity, likely resulting from the therapeutic enhancement of mucosal defense mechanisms against luminal antigens and pathogens[18]. The elevation of D-lactic levels in both groups indicates a modification in microbial fermentation processes, potentially signifying alterations in gut microbiota composition or activity. The significant elevation in ETX levels following therapy may suggest enhanced bacterial translocation or alterations in gut barrier permeability, warranting additional examination of the consequences of these changes on patient health. The research also emphasizes notable alterations in nutritional and inflammatory indicators, specifically SF, PA, and ALB, subsequent to treatment. The drop in SF levels following therapy may indicate less inflammation or changes in iron metabolism, potentially linked to the therapeutic approaches utilized[19,20]. The reduction in PA and ALB levels following therapy in both groups indicates an effect of the treatment on the patients' nutritional and inflammatory condition. The significant reductions in these markers within the control group may suggest a varied response to the treatment technique employed, maybe incorporating more aggressive or comprehensive therapeutic measures that could have unintentionally influenced nutritional status.

The reported results and their fundamental mechanisms can be situated within the larger context of stomach cancer treatment and management. The restoration of gastroesophageal junction integrity and the enhancement of gastrointestinal barrier function are essential for improving patient outcomes and quality of life following treatment. The changes in nutritional and inflammatory markers highlight the necessity of holistic patient care, which includes both the specific treatment of the primary ailment and the management of related systemic repercussions. The processes behind these reported changes require additional examination. The relationship among therapeutic interventions, gastrointestinal health, microbial equilibrium, and overall nutritional and inflammatory conditions is intricate[21]. The treatments likely influenced both the local gastric environment and had systemic effects, potentially mediated by gut-brain axis interactions, modifications in gut microbiota composition and function, and changes in systemic inflammatory pathways.

The observed elevation in D-lactic acid and ETX levels post-treatment, while seemingly contradictory to improved gastrointestinal barrier function, can be explained by postoperative physiological changes. D-lactic acid, a byproduct of gut bacterial fermentation, reflects shifts in microbial composition following surgical alterations like anastomosis. Similarly, increased ETX levels, indicative of bacterial translocation due to transient intestinal permeability changes, are common in the early postoperative phase after major gastrointestinal surgery. These fluctuations are not indicative of long-term barrier dysfunction but rather transient disruptions in gut integrity. The improvement in DAO levels, however, suggests a longer-term restoration of gastrointestinal barrier function, reinforcing the overall trend of recovery despite short-term microbiota shifts and permeability changes. In terms of surgical execution, all procedures were performed by surgeons with at least five years of clinical experience, minimizing potential biases related to surgical proficiency. A standardized protocol was strictly adhered to for both the FA and posterior wall anastomosis techniques, ensuring procedural consistency and the reliability of comparative analysis. No significant baseline differences were noted between the two groups, strengthening the validity of our findings. While the FA group exhibited substantial improvements in GERD symptoms, this did not immediately correlate with changes in nutritional markers such as SF, PA, and ALB. The complexity of the FA technique may delay nutritional recovery due to altered gastrointestinal dynamics, whereas the posterior wall anastomosis group demonstrated a more rapid recovery in nutritional status. This

suggests that while FA effectively mitigates GERD symptoms, its impact on nutritional recovery is more gradual, likely due to the intricacies of the reconstructive process and postoperative inflammatory response.

This study's limitations include a relatively small sample size, which may impact the generalizability of the findings. Additionally, the retrospective nature of the analysis could introduce selection biases and limit the ability to establish causality. The study also focused on short-term outcomes, leaving long-term effects of the anastomosis techniques on GER and patient quality of life unexplored. Furthermore, the limited postoperative assessment period (only on the first postoperative day) restricts our understanding of the sustained impact of the anastomosis techniques. Future studies should aim to expand the sample size and employ a prospective design to validate these findings. Long-term follow-up is crucial to assess the durability of the anastomosis techniques' effects on reflux control and overall survival rates. Additionally, incorporating extended follow-up periods will offer a more comprehensive understanding of the long-term effects on GERD symptoms, nutritional status, and overall patient outcomes. Investigating patient-reported outcomes will provide a more complete evaluation of the impact on quality of life.

CONCLUSION

In conclusion, the application of the Forearm Anastomosis technique in radical proximal gastrectomy for gastric cancer might demonstrate promising outcomes. It could effectively alleviate GER symptoms, enhance gastrointestinal barrier function, and improve nutritional status in patients. Further research is warranted to validate these findings and establish the technique as a standard practice in surgical management.

FOOTNOTES

Author contributions: Yang JL and Yang YJ contribute equally to this study as co-first authors; the authorship contributions for this study are as follows: Yang JL, Yang YJ, and Xu L were responsible for the conceptualization of the study; Data curation, formal analysis, and methodology were primarily conducted by Yang JL and Yang YJ; Both Yang JL and Yang YJ also contributed to the acquisition of resources and the use of software; The original draft of the manuscript was written by Yang JL and Yang YJ, while Xu L provided critical revisions during the writing and review process; all authors reviewed and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics committee of The First Affiliated Hospital of Soochow University.

Informed consent statement: Written informed consent for publication was obtained from all patients in this retrospective analysis.

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

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ORIGINAL ARTICLE

Retrospective Study

Retrospective analysis of preoperative tumor marker levels in rectal cancer patients: Implications for diagnosis

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Abstract

BACKGROUND

Early detection of rectal cancer poses significant challenges. Current diagnostic methods, including colonoscopy, imaging techniques, and fecal tests, have limitations such as invasiveness, cost, and varying sensitivity. This study evaluated the diagnostic value of preoperative serum tumor markers in rectal cancer patients.

AIM

To investigate the value of a multi-marker approach for the preoperative diagnosis of rectal cancer.

METHODS

A retrospective analysis of 250 patients diagnosed with rectal cancer between July 2022 and July 2024 was conducted. Preoperative alpha-fetoprotein levels, carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), CA19-9, CA15-3, and CA72-4 were analyzed. All blood samples were collected under standardized conditions, including fasting status and proper storage methods, within two weeks before surgery. Diagnostic performance was assessed using receiver operating characteristic curve analysis. Correlations among clinicopathological features were also evaluated.

RESULTS

CEA demonstrated the highest diagnostic performance among individual tumor markers with an area under the curve (AUC) of 0.78 [95% confidence interval (CI):

0.73-0.83]. However, a combination of CEA, CA19-9, and CA72-4 showed superior performance, achieving an AUC of 0.87 (95%CI: 0.83-0.91). Significant correlations were observed between CEA levels and several clinicopathological features, including tumor stage ($P < 0.001$), lymph node involvement ($P = 0.002$), and distant metastasis ($P < 0.001$). Furthermore, in a subgroup analysis of patients diagnosed after July 2022, the integration of fecal occult blood testing with the tumor marker panel (CEA + CA19-9 + CA72-4) significantly improved diagnostic accuracy, increasing the AUC to 0.91 (95%CI: 0.86-0.96).

CONCLUSION

A multimarker approach combining CEA, CA19-9, and CA72-4 with fecal occult blood testing enhances the preoperative assessment of patients with rectal cancer. These findings suggest potential improvements in risk stratification and management of patients with rectal cancer.

Key Words: Rectal cancer; Tumor markers; Carcinoembryonic antigen; Cancer antigen 19-9; Cancer antigen 72-4; Fecal occult blood test; Diagnosis

Core Tip: This study highlights the effectiveness of a multi-marker approach for the preoperative diagnosis of rectal cancer. Analysis of serum levels of the tumor markers carcinoembryonic antigen, cancer antigen 19-9, and cancer antigen 72-4, along with fecal occult blood testing, demonstrated improved diagnostic accuracy, with an area under the curve of 0.91. Significant correlations between elevated carcinoembryonic antigen levels and clinicopathological features, such as tumor stage and lymph node involvement, suggest that this combined strategy could enhance the risk stratification and management of patients with rectal cancer, ultimately aiding in earlier detection and better clinical outcomes.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide, with rectal cancer accounting for approximately one-third of all CRC cases[1]. Despite the advancements in diagnostic techniques and treatment modalities, rectal cancer continues to pose significant challenges in terms of early detection, accurate staging, and prognostic assessment. In this context, tumor markers have garnered considerable attention as a potential tool for improving patient management and outcomes. Tumor markers are biochemical substances cancer cells, or other cells produce in response to certain benign conditions. These markers can be found in blood, urine, or tissue samples, indicating the presence, progression, or response to cancer treatment. In the realm of rectal cancer, several tumor markers have been investigated for their diagnostic and prognostic value, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), CA19-9, CA15-3, and CA72-4.

AFP is normally produced in the liver and yolk sac of developing fetuses. Although it is primarily associated with liver and germ cell tumors, elevated levels have been reported in some gastrointestinal cancers, including rectal cancer. CEA is perhaps the most well-studied tumor marker in CRC. It is a glycoprotein involved in cell adhesion and is often elevated in various adenocarcinomas, particularly those of the gastrointestinal tract[2]. CA125 is traditionally associated with ovarian cancer but has also been investigated in other malignancies, including CRC[3]. CA19-9 is another widely studied marker initially developed for pancreatic cancer but is also elevated in other gastrointestinal malignancies[4]. CA15-3, which is primarily used for breast cancer monitoring, and CA72-4, which is associated with gastric cancer, have also shown potential utility in CRC[5].

Although these tumor markers have been studied individually in various contexts, their collective evaluation in a specific setting of rectal cancer, particularly in the preoperative phase, remains an area of active research. The limitations of current diagnostic methods highlight the need for more reliable and non-invasive biomarkers that can complement existing techniques. Preoperative assessment is crucial as it influences treatment decisions, surgical planning, and overall patient management. Moreover, the potential of these markers to provide prognostic information could significantly impact follow-up strategies and personalized treatment approaches. Recently, there has been a growing interest in combining multiple tumor markers to improve diagnostic accuracy. This approach, often called a tumor marker panel, aims to overcome the limitations of individual markers and provide a more comprehensive assessment of the disease state. Integrating novel markers or diagnostic tests, such as fecal occult blood test (FOBT), into these panels may enhance their clinical utility.

MATERIALS AND METHODS

Study design and patient selection

This retrospective study was conducted at Linquan County People's Hospital, China tertiary care center, and included patients diagnosed with rectal cancer between July 2022 and July 2024. Patients were systematically screened from the hospital information system based on the following inclusion criteria: Histologically confirmed rectal cancer, availability of preoperative serum tumor marker data for at least four of the six markers (AFP, CEA, CA125, CA19-9, CA15-3, and CA72-4), and completion of the necessary clinical and pathological assessments. The study protocol was approved by the Institutional Review Board of Linquan County People's Hospital, and the requirement for informed consent was waived because of the retrospective nature of the study. Patients were excluded if they had a history of other malignancies, received neoadjuvant therapy before blood sample collection, had incomplete medical records defined as missing key information (such as tumor marker levels or clinicopathological data), presented with synchronous tumors, or had a history of inflammatory bowel disease.

Data collection

Patient data were extracted from the electronic medical records and encompassed a comprehensive range of information. This included demographic details, such as age, sex, and body mass index; clinical characteristics, including tumor location and clinical stage (based on the 8th edition of the American Joint Committee on cancer tumor-node-metastasis staging system); and pathological features, such as histological type, differentiation grade, lymph node involvement, and presence of distant metastasis. Additionally, preoperative serum levels of tumor markers (AFP, CEA, CA125, CA19-9, CA15-3, and CA72-4) and FOBT results were collected. Treatment details were also recorded, including the type of surgery and adjuvant therapy. Finally, follow-up data, including the date of the last follow-up, recurrence, and survival status, were included to facilitate a comprehensive analysis.

Tumor marker analysis

Blood samples for tumor marker analysis were collected within two weeks before surgical intervention. The specific time window for sample collection was standardized to within two weeks before surgery. Additionally, all samples were collected under consistent conditions, including fasting status when required, and were processed and stored using standardized protocols. Serum tumor marker levels were measured using commercially available immunoassay kits according to the manufacturers' instructions. AFP, CEA, CA125, CA19-9, and CA15-3 levels were analyzed using a Siemens Atellica IM1600 automated immunoassay analyzer (Siemens Healthineers, Erlangen, Germany). CA72-4 levels were measured using a Roche Cobas e411 analyzer (Roche Diagnostics, Basel, Switzerland). The following cutoff values were used to define elevated levels based on the manufacturers' recommendations and institutional standards: AFP (8.1 ng/mL), CEA (5 ng/mL), CA125 (30.2 U/mL), CA19-9 (37 U/mL), CA15-3 (32.4 U/mL), and CA72-4 (6.9 U/mL). FOBT were performed using a guaiac-based test or fecal immunochemical test, with a positive result defined as ≥ 20 μg Hb/g feces.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, United States). Statistical significance was set at $P < 0.05$ for all analyses. Descriptive statistics were used to summarize the patient characteristics and tumor marker levels. Continuous variables are presented as the median and interquartile range or mean ± SD depending on the data distribution. Categorical variables are expressed as frequencies and percentages. The diagnostic performance of individual tumor markers and their combinations was evaluated using receiver operating characteristic curve analysis. The area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were calculated. The optimal cutoff values for each marker were determined using the Youden index.

The association between tumor marker levels and clinicopathological features was assessed using the χ^2 or Fisher's exact test for categorical variables and the Mann-Whitney U test or Kruskal-Wallis test for continuous variables. A Spearman's rank correlation coefficient was used to evaluate the correlation between tumor markers. Subgroup analysis was performed on patients diagnosed after July 2022 to assess the added value of FOBT. The diagnostic performances of the tumor marker panels with and without including FOBT results were compared using the DeLong test for AUC comparison.

Ethical considerations

This study followed the Declaration of Helsinki and the Good Clinical Practice guidelines. Patient confidentiality was maintained throughout data collection and analysis. All patient data were anonymized and de-identified before analysis.

RESULTS

Patient characteristics

A total of 250 patients with rectal cancer who met the inclusion criteria were included in this study. The median age of the cohort was 62 years (range: 35-85 years), and the male-to-female ratio was 1.4:1. Table 1 summarizes the demographic and clinicopathological characteristics of the study population.

Table 1 Demographic and clinicopathological characteristics of the study population characteristic

Characteristic	*n* (%)
Age, years	
< 60	98 (39.2)
≥ 60	152 (60.8)
Sex	
Male	146 (58.4)
Female	104 (41.6)
Tumor location	
Upper rectum	62 (24.8)
Middle rectum	103 (41.2)
Lower rectum	85 (34.0)
Clinical stage	
I	45 (18.0)
II	78 (31.2)
III	92 (36.8)
IV	35 (14.0)
Histological type	
Adenocarcinoma	228 (91.2)
Mucinous	18 (7.2)
Signet ring cell	4 (1.6)
Differentiation	
Well	32 (12.8)
Moderate	165 (66.0)
Poor	53 (21.2)

Tumor marker levels

The preoperative serum levels of the six tumor markers were analyzed in all patients. The median and proportion of patients with elevated levels of each marker are shown in Table 2. CEA showed the highest proportion of elevated levels (48.8%), followed by CA19-9 (24.8%) and CA72-4 (20.8%).

Diagnostic performance of tumor markers

The diagnostic performances of individual tumor markers and their combinations were evaluated using receiver operating characteristic curve analysis. Table 3 presents the AUC, sensitivity, specificity, positive predictive value, and negative predictive value for each marker and selected combinations. CEA demonstrated the highest individual diagnostic performance with an AUC of 0.78 [95% confidence interval (CI): 0.73-0.83]. The combination of CEA, CA19-9, and CA72-4 showed the best overall performance with an AUC of 0.87 (95%CI: 0.83-0.91).

Correlation with clinicopathological features

The association between tumor marker levels and clinicopathological features was also analyzed. Significant correlations were observed between CEA levels and tumor stage ($P < 0.001$), lymph node involvement ($P = 0.002$), and distant metastasis ($P < 0.001$). CA19-9 levels were significantly associated with tumor differentiation ($P = 0.018$) and distant metastasis ($P = 0.007$). CA72-4 levels significantly correlated with tumor size ($P = 0.013$) and lymph node involvement ($P = 0.009$). Table 4 presents the correlations between tumor marker levels and key clinicopathological features.

Subgroup analysis: FOBT

FOBT results were available for a subgroup of patients diagnosed after July 2022 ($n = 112$). The inclusion of FOBT in the tumor marker panel (CEA + CA19-9 + CA72-4 + FOBT) significantly improved the diagnostic performance compared to the panel without FOBT (AUC: 0.91, 95%CI: 0.86-0.96 *vs* AUC: 0.87, 95%CI: 0.81-0.93, $P = 0.028$). Table 5 presents the diagnostic performance of the tumor marker panel with and without FOBT. The addition of FOBT to the tumor marker panel increased the sensitivity from 81.2% to 86.5% and specificity from 77.8% to 82.3%.

Table 2 Preoperative serum levels of tumor markers tumor marker

Tumor marker	Median (IQR)	Elevated, *n* (%)
AFP (ng/mL)	3.2 (1.8-5.7)	18 (7.2)
CEA (ng/mL)	4.8 (2.3-12.6)	122 (48.8)
CA125 (U/mL)	16.5 (9.8-28.3)	45 (18.0)
CA19-9 (U/mL)	18.7 (8.9-42.1)	62 (24.8)
CA15-3 (U/mL)	15.3 (10.1-23.8)	28 (11.2)
CA72-4 (U/mL)	3.8 (1.9-8.2)	52 (20.8)

IQR: Interquartile range; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; CA: Cancer antigen.

Table 3 Diagnostic performance of tumor markers, %

Marker/combination	AUC (95%CI)	Sensitivity	Specificity	PPV	NPV
CEA	0.78 (0.73-0.83)	68.4	82.1	79.5	71.8
CA19-9	0.71 (0.65-0.77)	52.8	85.3	78.2	64.1
CA72-4	0.69 (0.63-0.75)	48.0	87.6	79.3	62.4
CA125	0.65 (0.59-0.71)	42.4	86.9	76.2	60.1
CA15-3	0.61 (0.55-0.67)	36.8	88.5	76.1	58.3
AFP	0.57 (0.51-0.63)	22.4	92.8	75.6	54.9
CEA + CA19-9	0.84 (0.79-0.89)	76.8	79.3	78.7	77.5
CEA + CA72-4	0.82 (0.77-0.87)	74.4	80.6	79.3	75.9
CEA + CA19-9 + CA72-4	0.87 (0.83-0.91)	81.2	77.8	78.5	80.6

AUC: Area under the curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; CEA: Carcinoembryonic antigen; CA: Cancer antigen; AFP: Alpha-fetoprotein.

Table 4 Correlation between tumor marker levels and clinicopathological features

Feature	CEA	CA19-9	CA72-4	CA125	CA15-3	AFP
Tumor stage	$P < 0.001$	$P = 0.032$	$P = 0.028$	$P = 0.145$	$P = 0.213$	$P = 0.678$
Lymph node involvement	$P = 0.002$	$P = 0.056$	$P = 0.009$	$P = 0.087$	$P = 0.312$	$P = 0.543$
Distant metastasis	$P < 0.001$	$P = 0.007$	$P = 0.019$	$P = 0.098$	$P = 0.176$	$P = 0.821$
Tumor differentiation	$P = 0.067$	$P = 0.018$	$P = 0.104$	$P = 0.231$	$P = 0.289$	$P = 0.765$
Tumor size	$P = 0.023$	$P = 0.041$	$P = 0.013$	$P = 0.156$	$P = 0.267$	$P = 0.612$

CEA: Carcinoembryonic antigen; CA: Cancer antigen; AFP: Alpha-fetoprotein.

DISCUSSION

This retrospective study evaluated the diagnostic value of preoperative serum tumor markers (AFP, CEA, CA125, CA19-9, CA15-3, and CA72-4) in patients with rectal cancer. Our findings highlight the potential utility of these markers, particularly when used in combination, to improve the preoperative assessment and management of patients with rectal cancer.

Diagnostic performance of tumor markers

CEA demonstrated the highest diagnostic performance among the individual tumor markers examined, with an AUC of 0.78. This finding is consistent with previous studies that established CEA as the most widely used tumor marker in CRC [2-6]. Our results showed that CA19-9 and CA72-4 also exhibited moderate diagnostic performance in rectal cancer, with

Table 5 Diagnostic performance of tumor marker panel with and without fecal occult blood test panel, %

Panel	AUC (95%CI)	Sensitivity	Specificity	PPV	NPV
CEA + CA19-9 + CA72-4	0.87 (0.81-0.93)	81.2	77.8	78.5	80.6
CEA + CA19-9 + CA72-4 + FOBT	0.91 (0.86-0.96)	86.5	82.3	83.1	85.8

AUC: Area under the curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; CEA: Carcinoembryonic antigen; CA: Cancer antigen; FOBT: Fecal occult blood test.

AUCs of 0.71 and 0.69, respectively. Although these markers are not routinely used for rectal cancer screening, their potential utility has been suggested in previous studies[4-6]. Our cohort's relatively low diagnostic performances of AFP, CA125, and CA15-3 suggest that these markers may have limited value as individual diagnostic tools for rectal cancer.

A key finding of our study is the improved diagnostic performance achieved by combining multiple tumor markers. The CEA, CA19-9, and CA72-4 panels demonstrated the highest AUC (0.87), significantly outperforming all the individual markers. This supports the growing body of evidence suggesting that multi-marker panels can enhance the detection and assessment of CRC. Compared to similar studies, our research utilized a broader range of tumor markers and included a larger sample size, which may account for the higher diagnostic performance observed. Additionally, including FOBT in our panel further distinguishes our study from previous studies. The synergistic effects of combining markers may be attributed to their different molecular origins and heterogeneity in tumor biology.

Correlation with clinicopathological features

Our analysis revealed significant correlations between certain tumor markers and clinicopathological features of rectal cancer. CEA levels are strongly associated with tumor stage, lymph node involvement, and distant metastasis. These findings align with previous studies reporting CEA as a valuable indicator of disease extent and metastatic potential in CRC[7]. The observed correlations between CA19-9 levels and tumor differentiation and distant metastasis suggest that this marker may provide additional information about tumor biology and behavior. Similarly, the association of CA72-4 with tumor size and lymph node involvement indicates its potential role in assessing the local tumor extent. These findings underscore the importance of considering multiple tumor markers in the preoperative evaluation of patients with rectal cancer, as they may offer complementary information on different aspects of tumor characteristics.

Integration of FOBT

A notable aspect of our study included FOBT results for patients diagnosed after July 2022. The addition of FOBT to the tumor marker panel (CEA + CA19-9 + CA72-4) significantly improved the diagnostic performance, increasing sensitivity and specificity. This finding is particularly relevant in recent efforts to enhance CRC screening strategies. While the FOBT, particularly the fecal immunochemical test, is primarily used for CRC screening in asymptomatic individuals[8], our results suggest that it may also be valuable in the diagnostic workup of suspected rectal cancer cases. The complementary nature of serum tumor markers and FOBT highlights the potential benefits of integrating multiple testing modalities to improve diagnostic accuracy.

Clinical implications

These findings have important clinical implications. Using a multi-marker panel (CEA + CA19-9 + CA72-4) in the preoperative assessment of patients with rectal cancer may improve diagnostic accuracy and provide a more comprehensive evaluation of tumor characteristics[9]. The strong prognostic value of preoperative CEA level supports its use in risk stratification and treatment planning, suggesting that patients with elevated CEA levels may benefit from more aggressive treatment strategies and closer postoperative surveillance. Furthermore, integrating FOBT with serum tumor markers offers a promising approach for enhancing the diagnostic workup of suspected rectal cancer cases, potentially leading to earlier detection and improved outcomes[10,11]. Compared to existing diagnostic methods, this multi-marker approach can be a non-invasive, cost-effective adjunct that complements imaging and endoscopic evaluations[12]. The observed correlations between tumor markers and clinicopathological features suggest that these markers may aid in the preoperative prediction of tumor stage and metastatic potential, potentially influencing decisions regarding neoadjuvant therapy or surgical approach. Collectively, these implications underscore the potential of tumor markers to significantly enhance the management and outcomes of patients with rectal cancer[13].

Limitations and future directions

Despite its contributions, this study had several limitations that warrant further acknowledgment. The study's retrospective nature introduces potential information biases, such as selection bias and missing data, which may have affected the validity of the findings. The single-center design may also restrict generalizability to other populations or healthcare settings. Several research directions could be pursued: (1) Conducting prospective, multicenter studies to validate the diagnostic value of the proposed multi-marker panel; (2) Investigating novel tumor markers or molecular signatures to enhance rectal cancer diagnosis accuracy; (3) Assessing the cost-effectiveness of integrating multiple tumor markers and FOBT into routine clinical practice; and (4) Exploring the potential role of tumor markers in monitoring treatment response and detecting recurrence in rectal cancer patients. Future studies should implement standardized data

collection protocols to mitigate information bias and consider using blinded assessments for tumor marker evaluation. These future endeavors will address the current limitations and advance our understanding and management of rectal cancer.

CONCLUSION

This retrospective study provides evidence of the utility of a multi-marker approach for the preoperative assessment of patients with rectal cancer. The combination of CEA, CA19-9, and CA72-4 demonstrated superior diagnostic performance compared with individual markers, and the addition of FOBT further improved diagnostic accuracy. These findings suggest that a comprehensive tumor marker panel, potentially including FOBT, could enhance the preoperative evaluation, risk stratification, and management of rectal cancer patients. Future prospective studies are needed to validate these results and explore their implementation in clinical practice, aiming to improve patient outcomes in rectal cancer.

FOOTNOTES

Author contributions: Li M and Yuan DH conceptualized this study; Yang Z and Yuan DH contributed to data collection; Zhang L and Lu TX drafted the initial manuscript and contributed to formal analysis; Li M, Yang Z, and Zhang L provided guidance for this study and contributed to the methodology and visualization; Lu TX and Yang Z validated the study; and all the authors participated in this study and jointly reviewed and edited the manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Linquan County People's Hospital (No. LQYY-2023-132).

Informed consent statement: The requirement for informed consent was waived because of the retrospective nature of the study.

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ORIGINAL ARTICLE

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Retrospective analysis of delta hemoglobin and bleeding-related risk factors in pancreaticoduodenectomy

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Abstract

BACKGROUND

Objective and accurate assessment of blood loss during pancreaticoduodenectomy (PD) is crucial for ensuring the safety and efficacy of the procedure. While the visual method remains the most common clinical metric, many scholars argue that it significantly differs from actual blood loss and is inherently subjective.

AIM

To assess blood loss in PD *via* delta hemoglobin (ΔHb) and compare it with the visual method to predict bleeding-related risk factors.

METHODS

In this retrospective analysis, 1722 patients who underwent PD from 2017 to 2022 at Shandong Provincial Hospital were divided into three groups: Open PD (OPD), laparoscopic PD (LPD), and conversion to OPD (CTOPD). Intraoperative ΔHb (IΔHb) was calculated *via* preoperative and 72-hour-postoperative hemoglobin concentrations, and its association with visually obtained estimated blood loss (EBL) was analyzed. Perioperative ΔHb (PΔHb) was calculated *via* preoperative and predischarge hemoglobin concentrations. We compared the differences in IΔHb and PΔHb among the three groups, and performed univariate and multivariate regression analyses of IΔHb and PΔHb.

RESULTS

The preoperative general information of patients showed no statistically significant difference among the three groups ($P > 0.05$). The IΔHb in the OPD,

LPD, and CTOPD groups were 22.00 (12.00, 36.00), 21.00 (10.00, 33.00), and 33.00 (18.12, 52.24) g/L, respectively; And the PΔHb in the OPD, LPD, and CTOPD groups were 25.87 (13.51, 42.00), 25.00 (14.00, 45.00), and 37.48 (21.64, 59.65) g/L, respectively, values significantly differed ($P < 0.05$). IΔHb and EBL were significantly correlated ($r = 0.337$, $P < 0.001$). The results of univariate and multivariate regression analyses indicated that American Society of Anesthesiologists (ASA) classification IV [95% confidence interval (CI): 2.330-37.811, $P = 0.049$] and preoperative total bilirubin > 200 μmol/L (95%CI: 2.805-8.673, $P < 0.001$) were independent risk factors for IΔHb ($P < 0.05$), and ASA classification IV (95%CI: 45.934-105.485, $P < 0.001$), body mass index > 24 kg/m² (95%CI: 1.285-9.890, $P = 0.011$), and preoperative total bilirubin > 200 μmol/L (95%CI: 6.948-16.797, $P < 0.001$) were independent risk factors for PΔHb ($P < 0.05$).

CONCLUSION

There is a correlation between IΔHb and EBL in PD, so we can assess the patients' intraoperative blood loss by the ΔHb method. ASA classification IV, body mass index > 24 kg/m², and preoperative total bilirubin > 200 μmol/L increased perioperative bleeding risk.

Key Words: Pancreaticoduodenectomy; Delta hemoglobin; Estimated blood loss; Postpancreatectomy hemorrhage; Risk factor

Core Tip: We collected the medical records of patients who underwent pancreaticoduodenectomy in Shandong Provincial Hospital from 2017 to 2022. We used the difference in hemoglobin concentration (delta hemoglobin) before and after surgery to assess the amount of perioperative bleeding in patients, compared with the estimated blood loss obtained by the visual method, and analyzed the correlation between the two. Moreover, univariate and multivariate regression analyses were performed on the patients' delta hemoglobin to predict risk factors related to bleeding.

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INTRODUCTION

Pancreaticoduodenectomy (PD) is a standard surgical procedure used to treat benign and malignant tumors, including pancreatic head cancer, duodenal cancer, and bile duct cancer. However, PD is regarded as one of the most complex and challenging surgeries in general surgery because of its extensive resection range, intricate gastrointestinal tract reconstruction, and high rate of postoperative complications[1]. With the development of laparoscopic technology, Gagner and Pomp[2] successfully performed the world's first laparoscopic PD (LPD) in 1994, after which LPD was gradually introduced into clinical practice and widely adopted. Compared with open PD (OPD), LPD is more technically challenging, and its safety and clinical outcomes remain uncertain[3]. The amount of intraoperative blood loss in PD patients is a crucial factor related to surgical safety and patient prognosis. Therefore, an accurate assessment of intraoperative blood loss is essential for smooth operation and postoperative recovery. There are various clinical methods for estimating blood loss[4,5], including visual estimation and calculation methods, but both are often unreliable and inaccurate. Despite its limitations, the visual estimation method remains the most commonly used approach in clinical practice. In this method, surgeons and anesthesiologists estimate blood loss on the basis of the amount collected in suction canisters, observe intraoperative bleeding, and determine the amount of blood absorbed by surgical gauze[5-8]. While this method is simple, quick, and easy to apply, it is highly subjective and susceptible to individual bias, making it difficult to accurately reflect actual intraoperative blood loss[9]. We used the difference between preoperative and postoperative hemoglobin (Hb) concentrations, accounting for intraoperative and postoperative transfusions, and introduced the concept of a modified delta Hb (ΔHb) to reflect bleeding in patients undergoing PD. The intraoperative bleeding analyzed included blood loss from before the start of the operation to 72 hours after the operation. Perioperative bleeding was defined as blood loss from before the start of the operation to discharge from the hospital.

In this study, we retrospectively analyzed the clinical data of 1722 patients who underwent PD from January 2017 to December 2022 at Shandong Provincial Hospital, assessed the amount of intraoperative bleeding and analyzed the risk factors associated with bleeding to provide new insights into comparing the clinical efficacy of different surgical procedures and reducing the risk of surgical bleeding.

MATERIALS AND METHODS

General information

In this study, we collected the clinical data of 1873 patients who successfully underwent PD at Shandong Provincial Hospital Affiliated to Shandong First Medical University from January 2017 to December 2022. After excluding 27 patients due to age, 111 patients who underwent combined resection of other organs, and 13 patients with missing test results, 1722 patients were ultimately included. The inclusion criteria were as follows: (1) Preoperative patients who underwent computed tomography, magnetic resonance imaging, ultrasound endoscopy, and other examinations for preliminary diagnosis; (2) Surgical indications for PD with no contraindications for surgery; (3) No invasion of the portal vein, mesenteric artery, inferior vena cava, *etc*, and no distant metastasis to organs such as the liver or abdominal cavity; (4) No insufficiency of vital organs, including the heart, lungs, brain, or kidneys; (5) Aged between 18 years and 80 years; and (6) Patient and family members signed the informed consent form for surgery. The exclusion criteria were as follows: (1) Cardiac, pulmonary, cerebral, or other functional insufficiencies; (2) Incomplete case data; and (3) Multiple-organ resections, such as combined hepatic, colonic, or superior mesenteric vessel resections. The patients were divided into three groups on the basis of the surgical method used: The OPD group (n = 511), the LPD group (n = 982), and the CTOPD group (n = 229). This study was approved by the Ethics Committee of Shandong Provincial Hospital, approval No. 2024-403.

Surgical methods

In patients who underwent LPD, the entire surgical procedure was performed laparoscopically. The main steps included the following: (1) Explore the abdominal cavity to identify any metastasis to the peritoneum or abdominal organs; (2) Isolate and resect the tumor and performing lymph node dissection; and (3) Reconstruct the digestive tract[10]. The surgical approach for OPD primarily involves classical PD. The methods for exploration, isolation, resection, and reconstruction of the digestive tract are essentially the same as those used in LPD. If intraoperative bleeding, severe adhesions, or a close relationship between the tumor and major blood vessels occurred during LPD, the laparoscopic operation was difficult, and conversion to open surgery was performed.

Definitions of relevant indicators

Intraoperative ΔHb (IΔHb) was defined as the difference between the preoperative Hb concentration and the Hb concentration within 72 hours after surgery plus the increase in the Hb concentration due to transfusion. Typically, patients' blood volume nearly returns to normal 72 hours after surgery, and the Hb concentration remains relatively stable[11]. Perioperative ΔHb (PΔHb) was defined as the difference between the preoperative Hb concentration and the predischarge Hb concentration plus the increase in the transfusion-induced Hb concentration. Intraoperative bleeding obtained *via* the visual method was termed estimated blood loss (EBL). The postpancreatectomy hemorrhage (PPH)-related grading criteria were based on the International Study Group of Pancreatic Surgery definitions[12].

Observation and analysis of indicators

Preoperative general data, including sex, age, body mass index (BMI), diabetes history, previous abdominal surgeries, preoperative alkaline phosphatase, preoperative glutamyl transpeptidase, preoperative Hb, American Society of Anesthesiologists (ASA) classification, and preoperative total bilirubin, were compared among the OPD, LPD, and CTOPD groups. The differences in IΔHb and PΔHb among these groups were also examined. The correlation between patients' IΔHb and EBL was analyzed. Univariate and multivariate regression analyses were conducted for IΔHb and PΔHb.

Formula

$\Delta Hb = Hb_{preop} - Hb_{postop}$ + infused Hb[13]; infused Hb = number of units transfused × 28/(BV/1000)[14]; Hb_{preop} (g/L): Patient's preoperative Hb concentration; Hb_{postop} (g/L): Hb concentration measured within 72 hours post-surgery or before discharge; if multiple test results were available within the first 72 hours postoperatively, the last result was selected for calculation; BV (mL): Patients' estimated blood volume calculated *via* the International Council for Standardization in Haematology formula[11].

Statistical analysis

SPSS statistical software (IBM SPSS Statistics, version 26.0; IBM Corporation, Armonk, NY, United States) was used to analyze and process the data in this study. Normally distributed data are expressed as the means ± SDs, and one-way analysis of variance was used to compare the three groups. Measurement data not conforming to a normal distribution are expressed as the medians (interquartile ranges), and the rank sum test was used for comparisons among the three groups. Count data are expressed as n (%), and comparisons among groups were made *via* the χ^2 test or Fisher's exact test. Univariate and multivariate analyses of ΔHb were conducted *via* linear regression. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Comparison of preoperative general information

In this study, we analyzed and studied the case data of 1722 patients in the Department of Hepatobiliary Surgery at Shandong Provincial Hospital Affiliated to Shandong First Medical University. The cohort included 1083 males and 639 females aged 61.0 (53.0, 67.0) years. Patients were divided into three groups based on the surgical method: The OPD group (n = 511), the LPD group (n = 982), and the CTOPD group (n = 229). The preoperative general characteristics of the patients in the three groups, including age, sex, BMI, comorbid conditions, preoperative alkaline phosphatase, preoperative glutamyl transpeptidase, preoperative Hb concentration, ASA classification, and preoperative total bilirubin, were not significantly different (P > 0.05), as shown in Table 1.

Comparison of mortality rates

The perioperative mortality rates of the three groups are shown in Table 2, and the total mortality rate of the 1722 patients in this study was 1.1%, with no statistically significant difference among the three groups (P > 0.05).

Comparison of EBL and ΔHb among the three groups

There was a statistically significant difference in EBL among the three groups (P < 0.05), with the LPD group having a median EBL of 50.0 (50.0, 200.0) mL, which was lower than that of the other two groups. For IΔHb, the results of 22.00 (12.00, 36.00) g/L in the OPD group and 21.00 (10.00, 33.00) g/L in the LPD group were similar, and both were lower than 33.00 (18.12, 52.24) g/L in the CTOPD group. Statistically significant differences were observed among the three groups (P < 0.05). Similarly, when the PΔHb values of the three groups were compared, the results of 25.87 (13.51, 42.00) g/L in the OPD group were similar to those of 25.00 (14.00, 45.00) g/L in the LPD group, and both were lower than those of 37.48 (21.64, 59.65) g/L in the CTOPD group. Statistically significant differences were also observed among the three groups (P < 0.05), as detailed in Table 3.

Analysis of the relationship between IΔHb and EBL

There was a correlation between IΔHb and EBL in this study (r = 0.337, P < 0.001), as shown in Table 4; thus, IΔHb can be used to assess intraoperative blood loss.

Comparison of IΔHb and PΔHb in patients

A comparison of IΔHb and PΔHb in patients who underwent PD revealed that PΔHb 27.00 (14.00, 45.49) g/L was slightly greater than IΔHb 22.00 (11.00, 36.00) g/L, and the difference between the two was statistically significant (P < 0.05), as shown in Table 5.

Analysis of risk factors affecting patient IΔHb

Univariate regression analysis of IΔHb: Twelve variables were included for univariate regression analysis of IΔHb. The results revealed that ASA classification IV, BMI > 24 kg/m^2, and preoperative total bilirubin > 200 μmol/L were identified as risk factors for IΔHb (P < 0.05), as detailed in Table 6.

Multivariate regression analysis of IΔHb: The statistically significant results were further analyzed *via* multifactorial linear regression analysis. This analysis revealed that ASA classification IV and preoperative total bilirubin > 200 μmol/L were independent risk factors for IΔHb (P < 0.05). These findings suggest that ASA classification IV and elevated preoperative total bilirubin levels (> 200 μmol/L) are associated with a higher risk of intraoperative hemorrhage, as detailed in Table 7.

Analysis of risk factors affecting patient PΔHb

Univariate regression analysis of PΔHb: For the study of PΔHb, we also included 12 variables for univariate regression analysis. The results revealed that ASA classification IV, BMI > 24 kg/m^2, and preoperative total bilirubin > 200 μmol/L were also risk factors for PΔHb (P < 0.05), as shown in Table 8.

Multivariate regression analysis of PΔHb: The above statistically significant results were then analyzed *via* multifactorial linear regression analysis, which revealed that ASA classification IV, BMI > 24 kg/m^2, and preoperative total bilirubin > 200 μmol/L were independent risk factors for PΔHb (P < 0.05), implying that they are associated with increased perioperative bleeding risk, as detailed in Table 9.

DISCUSSION

PD involves a large resection area, requiring the removal of part of the stomach, the entire duodenum, the upper part of the jejunum, part of the pancreas, the gallbladder, and the common bile duct. Additionally, the procedures include pancreaticoenteric anastomosis, bilioenteric anastomosis, and gastrointestinal anastomosis. These factors make PD surgery particularly challenging, leading to numerous unpredictable complications both during and after the operation. Since Gagner and Pomp[2] successfully completed the world's first LPD in 1994, it has gradually gained acceptance in clinical practice and is now widely performed. However, its clinical efficacy remains uncertain. A multicenter clinical trial

Table 1 Comparison of the general patient characteristics among the three groups, *n* (%)

Characteristic	OPD (*n* = 511)	LPD (*n* = 982)	CTOPD (*n* = 229)	*P* value
Sex				
Male	312 (61.1)	616 (62.7)	155 (67.7)	0.223
Female	199 (38.9)	366 (37.3)	74 (32.3)	-
Age (years), interquartile range	61 (54.0-67.0)	61 (53.0-67.0)	61 (52.0-69.0)	0.992
BMI (kg/m^2), interquartile range	23.83 (21.48-26.03)	23.69 (21.77-25.95)	23.68 (21.62-26.22)	0.997
History of abdominal surgery				
Yes	83 (16.2)	135 (13.7)	33 (14.4)	0.430
No	428 (83.8)	847 (86.3)	296 (85.6)	-
History of diabetes				
Yes	98 (19.2)	166 (16.9)	38 (16.6)	0.506
No	413 (80.8)	816 (83.1)	191 (83.4)	-
Preoperative alkaline phosphatase (U/L), interquartile range	301.0 (126.0-516.0)	283.5 (119.75-510.25)	246.0 (97.0-459.5)	0.079
Preoperative glutamyl transpeptidase (U/L), interquartile range	336.0 (84.0-801.0)	372.0 (78.5-806.5)	267.0 (45.0-716.0)	0.132
Preoperative Hb (g/L), interquartile range	127.0 (115.0-138.0)	126.0 (114.0-136.0)	125.0 (114.0-139.0)	0.696
Preoperative albumin (g/L), interquartile range	38.7 (35.4-41.7)	38.5 (35.5-41,4)	38.2 (34.8-41.2)	0.482
ASA classification				
I	2 (0.4)	3 (0.3)	0 (0)	0.905
II	358 (70.1)	701 (71.4)	160 (69.9)	-
III	147 (28.8)	274 (27.9)	68 (29.7)	-
IV	4 (0.8)	4 (0.4)	1 (0.4)	-
Preoperative total bilirubin (μmol/L), interquartile range	82.57 (17.65-197.68)	73.25 (17.97-204.36)	60.07 (14.91-204.55)	0.441

OPD: Open pancreaticoduodenectomy; LPD: Laparoscopic pancreaticoduodenectomy; CTOPD: Conversion to open pancreaticoduodenectomy; BMI: Body mass index; Hb: Hemoglobin; ASA: American Society of Anesthesiologists.

Table 2 Comparison of mortality rates among the three groups, *n* (%)

Characteristic	OPD (*n* = 511)	LPD (*n* = 982)	CTOPD (*n* = 229)	*P* value
Perioperative death				
Yes	4 (0.8)	13 (1.3)	2 (0.9)	0.598
No	507 (99.2)	969 (98.7)	227 (99.1)	-

OPD: Open pancreaticoduodenectomy; LPD: Laparoscopic pancreaticoduodenectomy; CTOPD: Conversion to open pancreaticoduodenectomy.

in the Netherlands aimed to assess the feasibility of LPD by comparing its clinical outcomes with those of OPD. Unfortunately, the trial was prematurely terminated because of the high mortality rate associated with LPD-related complications and safety concerns[15]. Currently, even in experienced high-volume pancreatic centers, the overall complication rate after PD remains 30%-50%[1]. The major complications of PD include bleeding, pancreatic fistula, biliary fistula, and abdominal infection[16]. However, the primary complication that poses the greatest threat to a patient's life is bleeding [17]. The volume of intraoperative blood loss is a vital factor for surgical safety and patient outcomes, making accurate assessment of blood loss and prediction of risk factors essential for surgeons' preoperative preparation and timely intervention.

There are several methods for estimating blood loss, which can be broadly categorized into two types: Visual methods and calculation methods[4]. The visual method is still widely used in clinical practice[6]. However, this method is based on the estimation of blood loss by the surgeon on the basis of personal experience combined with clinical manifestations,

Table 3 Comparison of estimated blood loss and delta hemoglobin among the three groups

Blood loss	OPD (*n* = 511)	LPD (*n* = 982)	CTOPD (*n* = 229)	*P* value
EBL (mL), interquartile range	200.0 (50.0-300.0)	50.0 (50.0-200.0)	200.0 (50.0-400.0)	< 0.001
IΔHb (g/L), interquartile range	22.00 (12.00-6.00)	21.00 (10.00-33.00)	33.00 (18.12-52.24)	< 0.001
PΔHb (g/L), interquartile range	25.87 (13.51-42.00)	25.00 (14.00-45.00)	37.48 (21.64-59.65)	< 0.001

OPD: Open pancreaticoduodenectomy; LPD: Laparoscopic pancreaticoduodenectomy; CTOPD: Conversion to open pancreaticoduodenectomy; EBL: Estimated blood loss; IΔHb: Intraoperative delta hemoglobin; PΔHb: Perioperative delta hemoglobin.

Table 4 Correlation analysis between intraoperative delta hemoglobin and estimated blood loss

Classification	Spearman correlation coefficient	*P* value
IΔHb (g/L)	-	-
EBL (mL)	0.337	< 0.001

EBL: Estimated blood loss; IΔHb: Intraoperative delta hemoglobin.

Table 5 Comparison of intraoperative delta hemoglobin and perioperative delta hemoglobin

Classification	ΔHb (g/L)	*Z* value	*P* value
IΔHb, interquartile range	22.00 (11.00-36.00)	-	-
PΔHb, interquartile range	27.00 (14.00-45.49)	-10.729	< 0.001

ΔHb: Delta hemoglobin; IΔHb: Intraoperative delta hemoglobin; PΔHb: Perioperative delta hemoglobin.

Table 6 Univariate regression analysis of intraoperative delta hemoglobin

Parameter	*B* value	95%CI	*P* value
Age ≥ 65 years	0.236	-2.429-2.901	0.862
History of diabetes	0.724	-2.658-4.107	0.674
History of abdominal surgery	-1.076	-4.721-2.569	0.563
Preoperative biliary drainage	-2.606	-5.948-0.735	0.126
ASA classification IV	19.236	1.420-37.052	0.034
BMI > 24 kg/m^2	2.605	0.031-5.179	0.047
Malignant tumor	-0.717	-4.380-2.946	0.701
Preoperative albumin < 35 g/L	1.834	-1.288-4.955	0.249
Pancreatic tumor	1.737	-0.973-4.447	0.209
Pancreatic carcinoma	2.041	-0.851-4.933	0.166
Ampulla of Vater carcinoma	-0.921	-5.055-3.214	0.662
Preoperative total bilirubin > 200 μmol/L	5.800	2.861-8.738	< 0.001

CI: Confidence interval; ASA: American Society of Anesthesiologists; BMI: Body mass index.

and the results are more subjective[9]. The calculation methods include techniques such as the weighing calculation method and the concentration calculation method. The weighing calculation method estimates blood loss by measuring the weight difference before and after surgery[18]. While it is more accurate than the visual method, it still has significant errors. The method for calculating concentration assesses blood loss by calculating the difference in Hb concentration or hematocrit between the preoperative and postoperative periods[19-21]. This method converts the change in these concen-

Table 7 Multivariate regression analysis of intraoperative delta hemoglobin

Parameter	*B* value	95%CI	*P* value
ASA classification IV	20.071	2.330-37.811	0.049
BMI > 24 kg/m^2	2.576	0.013-5.140	0.078
Preoperative total bilirubin > 200 μmol/L	5.739	2.805-8.673	< 0.001

CI: Confidence interval; ASA: American Society of Anesthesiologists; BMI: Body mass index.

Table 8 Univariate regression analysis of perioperative delta hemoglobin

Parameter	*B* value	95%CI	*P* value
Age ≥ 65 years	-0.293	-4.804-4.219	0.899
History of diabetes	-3.663	-9.385-2.060	0.210
History of abdominal surgery	3.798	-2.369-9.966	0.227
Preoperative biliary drainage	-4.268	-9.924-1.389	0.139
ASA classification IV	73.919	43.926-103.911	< 0.001
BMI > 24 kg/m^2	5.468	1.114-9.822	0.014
Malignant tumor	1.284	-4.916-7.485	0.685
Preoperative albumin < 35 g/L	0.778	-4.507-6.064	0.773
Pancreatic tumor	-0.076	-4.665-4.514	0.974
Pancreatic carcinoma	-0.469	-5.367-4.428	0.851
Ampulla of Vater carcinoma	1.670	-5.327-8.668	0.640
Preoperative total bilirubin > 200 μmol/L	11.975	7.011-16.938	< 0.001

CI: Confidence interval; ASA: American Society of Anesthesiologists; BMI: Body mass index.

Table 9 Multivariate regression analysis of perioperative delta hemoglobin

Parameter	*B* value	95%CI	*P* value
ASA classification IV	75.710	45.934-105.485	< 0.001
BMI > 24 kg/m^2	5.588	1.285-9.890	0.011
Preoperative total bilirubin > 200 μmol/L	11.872	6.948-16.797	< 0.001

CI: Confidence interval; ASA: American Society of Anesthesiologists; BMI: Body mass index.

trations into an estimate of blood loss. However, it overlooks potential variations in blood volume, Hb levels, and hematocrit among patients with different body weights, leading to a certain degree of bias. The concept of ΔHb was introduced by Hogervorst *et al*[22] in their analysis of the impact of Hb concentration reduction during cardiac surgery on postoperative adverse outcomes. Spolverato *et al*[13] introduced ΔHb into general surgery and reported that a postoperative ΔHb ≥ 50% was linked to an increased complication rate. This conclusion was drawn from an analysis of 4669 patients who underwent major abdominal surgeries, including hepatobiliary, pancreatic, and colorectal procedures. However, that study did not account for the impact of blood transfusions on ΔHb. Therefore, we applied this method to PD, incorporating the transfusion factor to derive a modified ΔHb, which provides a more accurate and objective assessment of blood loss during PD. Research indicates that patients require a minimum of 72 hours to mobilize sufficient plasma proteins to normalize intravascular blood volume following acute blood loss and that the Hb concentration stabilizes within 2-4 days after surgery[11,23]. Consequently, we used the Hb concentration at 72 hours postoperatively to calculate IΔHb.

In this study, the analysis of intraoperative blood loss revealed a correlation between IΔHb and EBL, indicating that IΔHb can be used to assess intraoperative blood loss effectively in PD patients. An analysis of the EBL obtained by the visual method in the three groups revealed that the results for the LPD group were lower than those for the other two groups. However, in major abdominal surgeries such as PD, where significant bleeding is common, visual methods often

underestimate actual blood loss. This method relies solely on the surgeon's and anesthesiologist's general judgment, making it subjective and potentially inaccurate[24,25]. Especially in laparoscopic surgery, substantial bleeding within the surgical field can hinder the surgeon's visibility and complicate the procedure. If the operation becomes too challenging to continue laparoscopically, it may be converted to open surgery. The inherent visual bias in estimating blood loss during laparoscopic procedures *via* the visual method often leads to an underestimation of the actual amount of bleeding [26]. In our study, the IΔHb values in the LPD, OPD, and CTOPD groups were 22.00 (12.00, 36.00) g/L, 21.00 (10.00, 33.00) g/L, and 33.00 (18.12, 52.24) g/L, respectively, with statistically significant differences among the three groups ($P < 0.05$). Compared with EBL, the intraoperative blood loss calculated *via* the ΔHb method was significantly greater. This discrepancy can be attributed to two main factors: The inaccuracy of the visual method, which tends to underestimate blood loss, and the use of Hb concentrations measured 72 hours postoperatively. This postoperative period includes not only intraoperative hemorrhage but also additional bleeding from gastrointestinal anastomoses, trauma oozing, stress ulcer bleeding, and other sources within 72 hours after surgery. Intraoperative blood loss was comparable between the OPD and LPD groups, with no statistically significant differences observed. Consistent with the findings of many other studies, LPD did not significantly increase the risk of intraoperative hemorrhage, demonstrating that it is as safe and effective as traditional OPD[27]. Intraoperative blood loss was significantly greater in the CTOPD group than in the other two groups. This can be attributed to the fact that during LPD, patients undergo immediate conversion to open surgery if intraoperative exploration reveals that the tumor is closely related to major blood vessels, making laparoscopic separation difficult, or if intraoperative hemorrhage is difficult to control, thereby compromising the surgical field and procedure. A study by Lof *et al*[28] identified age ≥ 75 years, pancreatic tumors, tumor size > 40 mm, and laparoscopic surgery as risk factors for conversion from LPD to open surgery. Pancreatic tumors, in particular, are more likely to require conversion than periampullary or duodenal tumors are, likely due to their anatomical proximity to major blood vessels[29]. This conversion is associated with an increased incidence of grade B/C PPH, higher 30-day mortality, and other adverse outcomes, which likely explains the greater degree of intraoperative bleeding observed in the CTOPD group. In our study, the conversion rate from LPD to open surgery was 18.9%, which is consistent with the 3.1%-24.6% conversion rates reported in other studies[30-33]. The overall mortality rate among the 1722 patients was 1.1%, which aligns with the 1%-2% mortality rates reported in previous studies[27,34]. There was no significant difference in mortality rates among the three groups, with the CTOPD group having a mortality rate of only 0.9%. This lack of increased mortality in the CTOPD group may be attributed to our proactive approach in converting to open surgery as soon as laparoscopic difficulties were identified, thereby ensuring patient safety.

We conducted univariate and multivariate regression analyses of IΔHb, identifying ASA classification IV and preoperative total bilirubin > 200 μmol/L as independent risk factors for IΔHb. The ASA classification, developed by the ASA, is a preanesthesia assessment tool that categorizes patients on the basis of their physical status and surgical risk, with higher grades indicating greater risk[35]. Studies have demonstrated that the ASA classification is a reliable predictor of postoperative complications, with higher ASA grades being significantly associated with an increased incidence of complications and mortality[36]. Wolters *et al*[37] examined the relationship between the ASA classification and perioperative risk factors in 6301 surgical patients and revealed a significant correlation between the ASA classification and intraoperative bleeding through univariate analysis. Intraoperative bleeding was shown to increase progressively from ASA grade I to grade IV. Consequently, accurate preoperative assessment of a patient's ASA classification is crucial for predicting intraoperative bleeding and enabling timely intervention.

Preoperative total bilirubin > 200 μmol/L was also an independent risk factor for IΔHb. Elevated bilirubin levels due to intrahepatic cholestasis from biliary obstruction lead to hepatic impairment, which in turn affects coagulation. Furthermore, obstructive jaundice is linked to a proinflammatory state caused by systemic endotoxemia, which compromises the body's immune function and inhibits intravascular coagulation[38]. Das *et al*[39] retrospectively analyzed the clinical data of patients who underwent PD between 2007 and 2018 and conducted both univariate and multivariate regression analyses of post-PD bleeding. Their findings indicated that elevated preoperative total bilirubin was an independent risk factor for bleeding in PD patients. Similarly, Wang *et al*[40] demonstrated that in patients with high preoperative bilirubin levels, performing preoperative biliary drainage (PBD) reduced inflammation, alleviated intrahepatic cholestasis, minimized hepatocellular injury, and improved coagulation factor levels and fibrinolytic processes. This intervention ultimately reduced the incidence of overall complications, including grade B/C PPH. Chen *et al*[41] also reported that routine PBD in patients with preoperative total bilirubin > 200 μmol/L could significantly reduce both the complication rate and mortality rate. On the basis of these findings, PBD should be routinely performed in such patients to effectively lower bilirubin levels and mitigate associated risks.

PPH is one of the more severe complications following PD. Although its incidence is lower than that of other complications, PPH remains a leading cause of poor postoperative outcomes. The current incidence of PPH ranges from approximately 3% to 16%, with a mortality rate between 11% and 38%[17,42,43]. PPH is primarily categorized into abdominal bleeding and gastrointestinal bleeding on basis of the bleeding site. However, regardless of the type, current methods only allow for approximate estimation or qualitative assessment rather than precise quantitative analysis. The International Study Group of Pancreatic Surgery classifies PPH into grades A, B, and C on the basis of factors such as the bleeding site, timing, severity, and other clinical considerations[12,44]. Patients with grade A PPH typically exhibit no significant clinical symptoms and have a favorable prognosis, generally not requiring special intervention. In contrast, patients with grade B or C PPH often experience a marked reduction in Hb levels and typically require blood transfusions, interventional embolization for hemostasis, or even additional surgery, which can be life-threatening[45]. The current classification of PPH severity mainly relies on the degree of decrease in the Hb concentration and the volume of blood transfusion during the bleeding episode. However, these criteria are not fully quantitative, leading to potential inaccuracies. Factors such as hemoconcentration at the time of bleeding can result in misleading Hb levels, potentially causing incorrect PPH classification and delays in treatment. For the above reasons, we utilized the ΔHb method and

measured the Hb concentration at 72 hours postoperatively and again before discharge. By this time, the patient's blood volume had typically returned to normal, and Hb levels had stabilized, making the calculations more accurate. This approach allows for a more objective and quantitative assessment of postoperative hemorrhage[11].

We also analyzed PΔHb and found that the differences among the three groups paralleled those observed in IΔHb, with significantly higher values in the CTOPD group than in the other two groups. The PΔHb [27.00 (14.00, 45.49) g/L] was slightly greater than the IΔHb [22.00 (12.00, 36.00) g/L] in the patients who underwent PD in this study. This suggests that perioperative hemorrhage primarily occurs during the operation and within the first 72 hours postoperatively, with a comparatively smaller decrease in the Hb concentration after the initial 72-hour period. Univariate and multivariate regression analyses of PΔHb identified ASA classification IV, BMI > 24 kg/m², and preoperative total bilirubin > 200 μmol/L as independent risk factors for PΔHb. Many researchers believe that a high preoperative BMI restricts the surgeon's maneuverability, increases surgical difficulty, and heightens the risk of bleeding. In 2004, Chang *et al*[46] identified high BMI as a predictor of intraoperative bleeding in radical prostatectomy. Similarly, Krane *et al*'s study [47] of 626 patients who underwent laparoscopic colorectal surgery reported a significant increase in intraoperative bleeding in overweight and obese patients. Moreover, Izumo evaluated the incidence and risk factors for PPH among 1169 patients who underwent pancreatectomy and found that a BMI ≥ 25 kg/m² was an independent risk factor for PPH after pancreatectomy, as determined by univariate and multivariate analyses[48]. Their conclusion was that higher BMI levels make surgeries more technically challenging, raising the likelihood of bleeding, which aligns with our findings.

In this research, we used an objective approach to access blood loss and examine bleeding risk factors in patients undergoing PD. However, there are several limitations to our study. Although the results obtained using this method may be influenced by factors such as rehydration, nutritional management, and others, in the vast majority of cases, the patient's blood volume stabilizes within 72 hours post-surgery. Therefore, this method remains an objective and accurate approach for assessing blood loss, especially when compared to the visual method. In addition, as a single-center retrospective analysis, selection bias may have influenced the data collection. Consequently, further multicenter randomized controlled and prospective studies are needed to validate the applicability of this method and to better guide its use in clinical practice.

CONCLUSION

In conclusion, assessing intraoperative blood loss *via* the ΔHb method is more objective and accurate than the visual method, with a demonstrable correlation between the two methods. This approach can be effectively applied to evaluate both intraoperative and perioperative blood loss in patients undergoing PD. Our univariate and multivariate regression analyses revealed that ASA classification IV, BMI > 24 kg/m², and preoperative total bilirubin > 200 μmol/L were significant risk factors for increased bleeding during hospitalization. To improve patient outcomes, surgeons should enhance preoperative preparations to mitigate these risks, thereby benefiting both treatment and prognosis.

FOOTNOTES

Author contributions: Lin YM designed the study, collected and analyzed data, and wrote the manuscript; Yu C participated in the study's conception, data collection, and assisted in writing the manuscript; Lin YM and Yu C they contributed equally to this article, they are the co-first authors of this manuscript; Xian GZ participated in study design and provided guidance; and all authors read and approved the final manuscript.

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Jia-Rui Liu, Jin Zhang, Xiang-Long Duan

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Abstract

BACKGROUND

The surgical management of rectal cancer is continuously advancing, with a current emphasis on minimising the need for a permanent stoma. Understanding the risk factors influencing sphincter preservation is crucial for guiding clinical decision-making and optimising preoperative patient evaluation.

AIM

To examine the risk factors influencing sphincter preservation in laparoscopic radical rectal cancer surgery.

METHODS

A retrospective analysis of the demographics, preoperative and intraoperative data, and pathological findings of 179 patients with rectal cancer who underwent laparoscopic radical rectal cancer surgery at our hospital between January 2022 and December 2023 was conducted. These clinical data were compared between two groups: Patients with sphincter preservation and those without, categorised as the sphincter-preserved and sphincter-unpreserved groups, respectively.

RESULTS
Of the 179 patients analysed, 150 were in the sphincter-preserved group and 29 were in the sphincter-unpreserved group. Tumour height was significantly greater in the sphincter-preserved group compared to the sphincter-unpreserved group. Conversely, elevated levels of carcinoembryonic antigen, carbohydrate antigen 19-9, and plasma D-dimer were significantly higher in the sphincter-unpreserved group. Significant differences were also observed between the two groups in terms of place of residence, presence of colonic polyps, neoadjuvant chemotherapy, preoperative radiotherapy, mucinous adenocarcinoma, nerve invasion, and tumour height. No significant differences were observed for other parameters. Logistic regression analysis identified colonic polyps, mucinous adenocarcinoma, nerve invasion, and tumour height as independent risk factors for sphincter preservation.

CONCLUSION
Several risk factors influencing sphincter preservation in laparoscopic radical rectal cancer surgery were identified. These factors could be valuable tools for guiding clinical decision-making and optimising preoperative patient evaluations.

Key Words: Rectal cancer; Laparoscopic surgery; Sphincter preservation; Risk factors; Preoperative evaluation

Core Tip: This study aimed to identify key risk factors associated with achieving tumour resection and sphincter preservation in patients with rectal cancer by analysing clinical data from 179 patients who underwent laparoscopic radical rectal cancer surgery. Patients with nerve invasion, mucinous adenocarcinoma, and tumours in the lower rectum were at higher risk of sphincter non-preservation. Logistic regression analysis identified nerve invasion, mucinous adenocarcinoma, and tumour height as independent risk factors for sphincter preservation. Conversely, sphincter preservation rates were higher among patients with concomitant colonic polyps. These findings provide valuable insights for identifying high-risk patients and guiding targeted interventions and preoperative evaluations.

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INTRODUCTION

Surgical resection remains the mainstay of treatment for rectal cancer (RC), with the primary objectives being complete tumour removal to minimise recurrence and maintain the patient's quality of life[1]. For most patients, the optimal surgical approach prioritises reducing the need for a permanent colostomy and achieving restorative anterior resection [2]. Laparoscopic techniques have gradually replaced traditional open surgery, becoming the preferred intervention for RC treatment[3]. However, undergoing abdominoperineal resection with a permanent colostomy poses significant physical, psychological, and economic challenges for patients, often making it challenging to accept[4]. Sphincter preservation is, therefore, a critical clinical concern. Identifying factors influencing sphincter preservation is essential to enhance awareness of the risk of permanent stoma and to guide more effective clinical interventions and preoperative assessments [5]. This study analysed and compared the clinical data of the included patients to identify risk factors affecting sphincter preservation in patients with RC undergoing laparoscopic radical surgery.

MATERIALS AND METHODS

Inclusion and exclusion criteria

The clinical data of 179 patients who underwent laparoscopic radical RC surgery at our hospital between January 2022 and December 2023 were retrospectively analysed.

Inclusion criteria: Patients diagnosed with rectal malignancy who underwent laparoscopic radical RC surgery.

Exclusion criteria: Patients with non-primary tumours and other cancerous lesions; open surgery; metastatic disease; incomplete tumour resection; and incomplete clinical data.

This study was conducted in accordance with the Declaration of Helsinki. Preoperative informed consent was obtained from all patients and their families. The study was approved by the Ethics Committee of Shaanxi Provincial People's

Hospital.

Data collection

The hospital information system was used to obtain the following patient-related information:

Basic information: Sex, age, place of residence, body mass index, history of previous abdominal surgery, history of recent aspirin use, smoking history, alcohol consumption history, time since onset of first symptoms or diagnosis, degree of tumour differentiation, and tumour-node-metastasis stage.

Preoperative variables: Duration of preoperative care, bowel preparation time, neoadjuvant chemotherapy, and preoperative radiotherapy.

Preoperative comorbidities: History of hypertension, diabetes mellitus, coronary artery disease, colonic polyps, rectal polyps, tumours causing obstruction, tumours with bleeding, peripheral vascular lesions of the lower extremities, hypoproteinaemia, anaemia, and fever of ≥ 37 °C.

Other clinical parameters: Pelvic effusion, tumour height, maximum transverse tumour diameter, American Society of Anaesthesiologists grading, nerve invasion, vascular invasion, and mucinous adenocarcinoma.

Preoperative biochemical indicators: White blood cells, platelets, albumin, glucose, serum potassium, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), prothrombin time, and D-dimer levels.

Statistical analysis

Data analysis was performed using SPSS 27.0 software. The normality of the measurement data was determined using the Shapiro-Wilk test. Normally distributed data are presented as the mean ± SD, while data with skewed distributions are expressed as M (P25, P75). Between-group comparisons were performed using the Mann-Whitney *U* test or independent samples *t*-test, as appropriate. Categorical data are expressed as *n* (%) and analysed using the χ^2 test. Logistic regression analysis was used to identify risk factors affecting sphincter preservation in patients undergoing laparoscopic radical RC surgery, with a significance level set at $\alpha = 0.05$.

RESULTS

Analysis of patients undergoing laparoscopic radical RC surgery

A total of 199 patients were initially considered for the study. However, six cases were excluded due to incomplete tumour resection and positive pathological margins; 13 cases were excluded due to palliative surgery resulting from distant metastasis or the presence of other cancerous lesions; and one case was excluded due to the need for intermediate open surgery due to severe abdominal adhesions.

Among the remaining 179 patients with RC included in the study, 150 underwent sphincter preservation, while 29 had sphincter removal, all performed through laparoscopic radical surgery. The clinical data of the sphincter-preserved group and the sphincter-unpreserved group were subsequently analysed.

Comparison of clinical data between the two groups

The sphincter-preserved group and the sphincter-unpreserved group were comparable in terms of baseline characteristics. However, statistically significant differences were observed between the two groups regarding tumour height, serum markers (CEA and CA19-9), place of residence, presence of comorbid colonic polyps, neoadjuvant chemotherapy, and nerve invasion.

Most of the patients in the sphincter-unpreserved group were from rural areas and had tumours in the lower to middle rectum. This group also exhibited a higher prevalence of nerve invasion and concomitant mucinous adenocarcinoma. In contrast, most patients in the sphincter-preserved group had tumours in the upper rectum and were more likely to have combined colonic polyps (Table 1). Furthermore, CEA and CA19-9 Levels were significantly higher in the sphincter-unpreserved group compared to the sphincter-preserved group ($P < 0.05$).

Logistic regression analysis of sphincter preservation in laparoscopic radical RC surgery

To evaluate whether the factors that differed significantly between the sphincter-preserved and sphincter-unpreserved groups were significant risk factors for sphincter preservation in laparoscopic radical RC surgery, logistic regression analyses were conducted. Sphincter preservation was used as the dependent variable (0 = unpreserved sphincter, 1 = preserved sphincter), while variables with significant differences ($P < 0.1$) in Table 1 were included as independent variables. The results indicated that the presence of colonic polyps, mucinous adenocarcinoma, nerve invasion, and tumour height were independent risk factors influencing sphincter preservation in laparoscopic radical RC surgery ($P < 0.05$; Table 2).

Table 1 Comparison of clinical data between sphincter-preserved and sphincter-unpreserved groups, *n* (%)

Factors	Sphincter-preserved group (*n* = 150)	Sphincter-unpreserved group (*n* = 29)	Statistics	*P* value
Age (years)	67 (59, 72)	65 (57, 73)	0.719	0.472
Sex			0.001	0.985
Male	98 (65.3)	19 (65.5)		
Female	52 (34.7)	10 (34.5)		
Residence			3.951	0.047
Rural	63 (42.0)	18 (62.1)		
Urban	87 (58.0)	11 (37.9)		
BMI (kg/m^2)	22.8 ± 3.2	22.5 ± 3.3	0.587	0.558
Time since onset of first symptoms or diagnosis (months)	2 (1, 6)	3 (2, 7)	1.225	0.220
Duration of preoperative care (days)	7 (5, 9)	7 (6, 10)	0.925	0.355
Preoperative bowel preparation time (days)	6 (4, 7)	6 (5, 7)	0.731	0.465
Colonic polyps	72 (48.0)	8 (27.6)	4.097	0.043
Rectal polyps	20 (13.3)	1 (3.4)	1.438	0.230
Tumours with bleeding	107 (71.3)	20 (69.0)	0.066	0.797
Tumours causing obstruction	22 (14.7)	1 (3.4)	1.821	0.177
Neoadjuvant chemotherapy	20 (13.3)	10 (34.5)	6.349	0.012
Preoperative radiotherapy	16 (10.7)	7 (24.1)	2.827	0.093
History of hypertension	53 (35.3)	12 (41.4)	0.384	0.535
Diabetes mellitus	22 (14.7)	7 (24.1)	0.984	0.321
Coronary artery disease	24 (16.0)	2 (6.9)	0.972	0.324
Peripheral vascular lesions of the lower extremities	11 (7.3)	5 (17.2)	1.840	0.175
History of previous abdominal surgery	41 (27.3)	6 (20.7)	0.554	0.457
History of recent aspirin use	22 (14.7)	3 (10.3)	0.104	0.747
Smoking history	26 (17.3)	6 (20.7)	0.186	0.666
Alcohol consumption history	20 (13.3)	3 (10.3)	0.019	0.891
Preoperative hypoproteinemia	17 (11.3)	5 (17.2)	0.334	0.563
Preoperative anemia	13 (8.7)	5 (17.2)	1.141	0.285
Pelvic effusion	48 (32.0)	8 (27.6)	0.220	0.639
Clinical stage			1.383	0.240
0/I/II	95 (63.3)	15 (51.7)		
III/IV	55 (36.7)	14 (48.3)		
Tumour T stage			0.030	0.863
Tis/T1/T2	49 (32.7)	9 (31.0)		
T3/T4	101 (67.3)	20 (69.0)		
N stage			0.390	0.532
N-	87 (58.0)	15 (51.7)		
N+	63 (42.0)	14 (48.3)		
Degree of tumour differentiation			4.003	0.144

Medium differentiation	124 (82.7)	22 (75.9)		
High differentiation	17 (11.3)	2 (6.9)		
Low differentiation	9 (6.0)	5 (17.2)		
Mucinous adenocarcinoma	14 (9.3)	7 (24.1)	3.813	0.051
Vascular invasion	38 (25.3)	7 (24.1)	0.018	0.892
Nerve invasion	75 (50.0)	22 (75.9)	6.548	0.011
Preoperative fever of ≥ 37 °C	31 (20.7)	10 (34.5)	2.627	0.105
ASA grading			0.283	0.595
I/II	112 (74.7)	23 (79.3)		
III/IV	38 (25.3)	6 (20.7)		
Tumour height			69.652	< 0.001
Upper rectum	55 (36.7)	1 (3.4)		
Middle rectum	73 (48.6)	2 (6.9)		
Lower rectum	22 (14.7)	26 (89.7)		
Maximum transverse tumour diameter (cm)	3.5 (2.8, 4.6)	3.8 (3.2, 4.4)	0.502	0.616
CEA (ng/mL)	3.25 (1.60, 10.55)	5.79 (3.21, 10.41)	2.444	0.015
CA19-9 (ng/mL)	13.65 (8.02, 21.43)	21.61 (12.28, 24.80)	2.299	0.022
ALB (g/L)	38.0 ± 4.1	38.0 ± 3.8	0.001	0.999
GLU (mmol/L)	4.89 (4.35, 5.63)	5.24 (4.61, 5.33)	0.849	0.396
Potassium (mmol/L)	3.9 (3.7, 4.2)	3.9 (3.8, 4.2)	0.527	0.598
PT-T (second)	12.3 (11.6, 12.9)	12.3 (11.7, 12.6)	0.031	0.975
DD (mg/L)	0.77 (0.62, 1.11)	0.88 (0.72, 1.72)	1.874	0.061
WBC (10^9/L)	5.38 (4.54, 6.41)	5.75 (5.07, 5.82)	1.106	0.269
PLT (10^9/L)	203 (166, 239)	204 (188, 222)	0.672	0.502

BMI: Body mass index; TNM: Tumour-node-metastasis; ASA: American Society of Anaesthesiologists; CEA: Carcinoembryonic antigen; ALB: Albumin; GLU: Glucose level; PT-T: Prothrombin time; DD: D-dimer levels; WBC: White blood cell count; PLT: Platelet count.

DISCUSSION

RC accounts for approximately one-third of all colorectal cancer (CRC) cases, which is the third most common cancer worldwide[6]. Early detection followed by surgical resection significantly improves survival outcomes for patients with RC[7]. Laparoscopic surgery has become an increasingly preferred minimally invasive approach for treating RC, with radical resection remaining the cornerstone of therapy[8]. Advances in preoperative neoadjuvant therapies, laparoscopic techniques, and the adoption of the principles of total mesenteric excision and circumferential resection margin have demonstrated that a distal resection margin of 1 cm does not compromise oncologic safety in RC[9]. These advancements have contributed to a higher rate of sphincter-preserved surgeries and low anastomoses[10-12]. More patients are now undergoing sphincter-preserving procedures with colorectal or coloanal anastomoses, offering the potential benefit of avoiding a permanent stoma. Improvements in surgical techniques and adjuvant therapies have reduced the frequency of abdominoperineal resections (APRs), supporting minimally invasive surgery and the restoration of gastrointestinal continuity[13,14]. A low stoma rate is considered an indicator of high surgical quality. Permanent colostomies not only alter the original anatomy of the colon but also disrupt bowel continuity, necessitate lifelong stoma care, and negatively impact the patient's body image and quality of life[15]. The current surgical focus is on preserving function while achieving radical tumour resection, with efforts aimed at avoiding permanent stomas whenever possible. This study attempts to determine whether other factors besides the distance of the lower tumor margin from the anal verge and the invasion of the anal canal by cancerous tissue affect sphincter preservation, exploring risk factors that may influence sphincter preservation.

The relationship between tumour height and sphincter preservation has been critically evaluated[16]. A smaller distance between the tumour and the anal verge, as well as a low tumour location, significantly increases the risk of sphincter removal in patients with RC. These factors heighten the likelihood of tumour invasion into the anal canal and the spread of cancerous tissue to the sphincter. In such cases, APR is often chosen to ensure complete resection, minimise postoperative recurrence, and achieve the goals of surgery[17]. However, the decision to perform sphincter-preserving

Table 2 Logistic regression analysis of sphincter preservation in laparoscopic radical rectal cancer surgery

Variable	β	*P* value	OR	95%CI
Residence	-1.046	0.131	0.351	0.090-1.367
Colonic polyps	-2.207	0.006	0.110	0.023-0.535
Neoadjuvant chemotherapy	1.848	0.302	6.347	0.190-211.759
Preoperative radiotherapy	0.807	0.674	2.241	0.052-95.916
Mucinous adenocarcinoma	2.504	0.009	12.230	1.847-80.999
Nerve invasion	1.836	0.012	6.272	1.499-26.247
Tumour height				
Upper rectum			Refence	
Middle rectum	-0.301	0.837	0.740	0.042-13.001
Lower rectum	5.292	< 0.001	198.820	13.665-2892.686
CEA	0.021	0.390	1.021	0.974-1.070
CA19-9	0.015	0.240	1.015	0.990-1.041
DD	0.013	0.755	1.013	0.934-1.099

TNM: Tumour-node-metastasis; CEA: Carcinoembryonic antigen; DD: D-dimer levels; OR: Odds ratio; CA19-9: Carbohydrate antigen 19-9.

surgery rather than APR involves careful consideration of multiple factors. These include the response of the tumour to radiotherapy, the feasibility of achieving complete tumour clearance, the patient's functional status and comorbidities [18]. Advances in surgical anastomoses and the use of neoadjuvant radiochemotherapy have improved the rates of sphincter preservation in cases of low and intermediate RC[19]. In selected patients, partial intersphincter resection can avoid radical colostomy, although its oncological outcomes remain controversial[20]. Despite these advancements, a significant number of patients with RC still face challenges related to unsuccessful sphincter preservation. Notably, there is a lack of studies that specifically identify potential factors influencing laparoscopic sphincter preservation during radical resection. Previous studies have suggested that neoadjuvant therapy might impair anorectal function; however, for patients with very low RC, neoadjuvant therapy could reduce tumour size, decrease the need for excessive bowel resection, and increase the likelihood of sphincter preservation[21]. The German RC Trial further highlighted that sphincter preservation was more frequent in patients who received preoperative radiotherapy, implying that tumour shrinkage plays a crucial role in avoiding permanent colostomy. It remains unclear whether neoadjuvant therapy directly enhances the chances of sphincter preservation or simply influences the surgeon's inclination to perform such procedures [22].

Nerve invasion refers to the pathological phenomenon where tumour cells infiltrate neural structures and spread along the nerve sheath. It is categorised by the extent of tumour involvement, including invasion of the nerve lining, neuronal sheath, and nerve tunica albuginea, or tumour cells encircling at least one-third of the nerve tunica albuginea layer[23, 24]. The identification of nerve invasion is based on microscopic examination of biopsy specimens by pathologists. Nerve invasion serves as a significant pathological indicator and prognostic factor in patients with RC. Patients with nerve invasion typically exhibit decreased overall survival, increased local recurrence, and increased metastatic disease[25]. This pathological feature is associated with more advanced disease RC nerve invasion. Preoperative prediction of nerve invasion status could help in personalising treatment strategies. Recent studies suggest that clinical imaging histology models based on preoperative magnetic resonance imaging (MRI) radiomic features combined with clinical risk factors can noninvasively predict nerve invasion, enabling tailored treatment approaches for patients with RC. Nerve invasion is not limited to tumour cell infiltration and growth along neural pathways; it also involves interactions between tumour cells and neurotrophic and chemokine factors released from the surrounding microenvironment. These interactions contribute to tumour invasion, local recurrence, and metastasis, leading to a poorer prognosis[26,27]. However, the influence of nerves and nerve signals on the tumour microenvironment remains poorly understood, and the role of neurogenesis in CRC remains unclear. In this study, nerve invasion was associated with a lower likelihood of sphincter preservation. Therefore, RC patients with nerve invasion might benefit from more aggressive preoperative interventions.

Rectal mucinous adenocarcinoma is a histological subtype of RC that accounts for 5%-15% of RC cases. It is characterised by the presence of abundant extracellular mucin within the tumour, constituting over 50% of the adenocarcinoma tumour stroma, as determined through histopathological examination[28]. Mucinous tumours exhibit distinct molecular features compared to non-mucinous tumours and can be reliably identified by T2-weighted MRI, which highlights the large, high-signal pools of mucin. This subtype is associated with an abnormal molecular background and aggressive biological behaviour, making patients more susceptible to metastasis and local recurrence. Compared to non-mucinous rectal adenocarcinomas, mucinous adenocarcinomas present a higher risk of local recurrence and reduced overall survival. While adjuvant chemotherapy for patients undergoing radical surgery might improve patient survival rates [29], mucinous adenocarcinomas often demonstrate resistance to neoadjuvant chemotherapy, resulting in treatment

failure. This resistance is attributed to the physical barrier created by mucin and the hypoxic environment, both of which reduce the efficacy of chemoradiotherapy. Studies focusing on the molecular differences between mucinous and non-mucinous adenocarcinomas could pave the way for the development of tailored chemotherapeutic agents for this subgroup of patients[30-32]. Improving outcomes for patients with mucinous adenocarcinomas necessitates a more individualised approach to therapy. This includes optimising neoadjuvant treatment regimens, implementing more effective preoperative adjuvant chemotherapy, and intensifying treatment for patients with associated risk factors. These strategies aim to reduce the likelihood of sphincter preservation failure.

Colonic polyps are defined as masses protruding into the lumen of the colon, with their histological classification primarily distinguishing between neoplastic and non-neoplastic polyps[33]. Non-neoplastic polyps, which are not associated with developmental abnormalities, include hyperplastic, juvenile, inflammatory, and dysmorphic lesions. Conversely, adenomatous polyps are precancerous lesions whose identification and removal could prevent the onset of CRC. Colonoscopy, often combined with endoscopic mucosal resection, is a safe and highly effective method for diagnosing, treating, and monitoring rectal lesions. Colonoscopy and polypectomy are effective preventive methods for managing precancerous lesions and reducing CRC-related mortality[34,35]. In this study, patients who underwent sphincter-preserving surgery had more comorbid colonic polyps. Adenoma progression typically occurs gradually, allowing diagnostic studies to play a critical role in early detection. Through endoscopic and imaging techniques, new heterochronous rectal tumours can be identified early, including asymptomatic lesions. This enables timely radical resection with sphincter preservation in cases where RC remains in situ, minimising the risk for radical surgeries. Future analytical studies should focus on further understanding the aetiology and pathogenesis of RC in patients with coexisting colonic polyps that have a wide range of genetics, environmental exposures, and associated factors that may modulate disease risk[36].

Treatment options for patients with RC, particularly those with low RC, have become increasingly complex. For patients with tumours that are easily resectable, preoperative radiotherapy might be used to achieve a complete clinical response, a controversial approach known as nonoperative treatment or deferred surgery[37]. Although laparoscopic surgery offers the advantage of magnified visualization, the surgical maneuver is more challenging. Surgeons must navigate risks such as incomplete tumour resection, poor anastomotic blood supply, and inadvertent sphincter injury, all of which may lead to sphincter preservation failure. Therefore, these complex procedures should be performed by highly experienced colorectal surgeons[38,39]. This study is the first to analyse potential risk factors affecting sphincter preservation in laparoscopic radical RC surgery, offering valuable insights for preoperative assessment, targeted interventions, and patient monitoring. Despite the importance of these factors, studies examining their impact on sphincter preservation in RC surgery remain limited.

This study has several limitations. First, as a retrospective analysis, it is inherently susceptible to selection bias and the influence of unmeasured confounders. Second, this study was conducted at a single centre, which might limit the generalisability of the findings to the broader patient population. Third, the analysis of risk factors did not encompass all potential factors that could impact sphincter preservation in laparoscopic surgery. To address these limitations, future research should include larger sample sizes and prospective, multicentre cohort studies to provide more comprehensive and generalisable insights.

CONCLUSION

Several risk factors were identified in patients with RC that influence successful tumour resection and sphincter preservation. These findings can aid in identifying high-risk patients, enabling targeted preoperative assessments and interventions. Addressing these risk factors through targeted interventions might help minimise the risk of sphincter damage during radical surgery. Further investigation is needed to better understand the influence of preoperative factors on sphincter preservation in patients with RC. In conclusion, this study identified independent risk factors affecting sphincter preservation in laparoscopic radical RC surgery, including nerve invasion, mucinous adenocarcinoma, colonic polyps, and tumour height. Evaluation of these risk factors could enhance the awareness of sphincter preservation and improve surgical outcomes in patients with RC.

FOOTNOTES

Author contributions: Liu JR and Duan XL designed the research study; Liu JR, Zhang J, and Duan XL conducted the research; Liu JR and Duan XL participated in the investigation and contributed to the methodological framework; Duan XL directed the research; Zhang J contributed to the visualization of this study; Liu JR and Duan XL performed data analysis and drafted the manuscript; All authors reviewed and approved the final version of the manuscript.

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ORIGINAL ARTICLE

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Clinical effect and prognosis of laparoscopic surgery on colon cancer complicated with intestinal obstruction patients

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Abstract

BACKGROUND

Colon cancer is one of the most common malignancies of the digestive tract, often complicated by intestinal obstruction, which can significantly impact patient outcomes. While traditional laparotomy is the standard treatment, it is associated with large wounds, slower recovery, and higher complication rates. Laparoscopic surgery, a minimally invasive approach, may offer better outcomes for these patients.

AIM

To evaluate the clinical effects and prognosis of laparoscopic surgery in patients with colon cancer complicated by intestinal obstruction compared to traditional laparotomy.

METHODS

A retrospective analysis was conducted on 100 patients diagnosed with colon cancer and intestinal obstruction who underwent surgical treatment between January 2020 and December 2022. Patients were divided into two groups: The control group (CG), treated with traditional laparotomy, and the observation group (OG), treated with laparoscopic surgery. Clinical effects, surgical indicators, postoperative pain, inflammatory response, complication rates, quality of life, and prognosis were assessed and compared between the two groups.

RESULTS

The OG showed superior clinical outcomes compared to the CG ($P < 0.05$). Patients in the OG had shorter operation times, reduced intraoperative blood loss, faster recovery of intestinal function, earlier mobilization, and shorter hospital stays ($P < 0.05$). Postoperative pain (numerical rating scale scores) and inflammatory markers [tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP)] were lower in the OG ($P < 0.05$). The incidence of complications was significantly reduced in the OG (6.00% *vs* 22.00%, $P < 0.05$). Quality of

life scores, including physical function, psychological state, social communication, and self-care ability, were significantly higher in the OG ($P < 0.05$). There were no significant differences between groups in abdominal drainage volume, 1-year tumor recurrence or metastasis rates, or 1- and 3-year survival rates ($P > 0.05$).

CONCLUSION

The OG showed superior clinical outcomes compared to the CG ($P < 0.05$). Patients in the OG had shorter operation times, reduced intraoperative blood loss, faster recovery of intestinal function, earlier mobilization, and shorter hospital stays ($P < 0.05$). Postoperative pain (NRS scores) and inflammatory markers (TNF-α, IL-6, CRP) were lower in the OG ($P < 0.05$). The incidence of complications was significantly reduced in the OG (6.00% *vs* 22.00%, $P < 0.05$). Quality of life scores, including physical function, psychological state, social communication, and self-care ability, were significantly higher in the OG ($P < 0.05$). There were no significant differences between groups in abdominal drainage volume, 1-year tumor recurrence or metastasis rates, or 1- and 3-year survival rates ($P > 0.05$).

Key Words: Colon cancer; Intestinal obstruction; Laparoscopic surgery; Complication

Core Tip: Laparoscopic surgery offers significant advantages for patients with colon cancer complicated by intestinal obstruction. Compared to traditional open surgery, it results in better clinical efficacy, reduced operation time, less intraoperative blood loss, faster recovery of intestinal function, and shorter hospital stays. Patients experience less postoperative pain, lower levels of inflammatory markers, fewer complications, and improved quality of life. These findings suggest that laparoscopic surgery is an effective and safe alternative, promoting better recovery and outcomes for this patient population.

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INTRODUCTION

Colon cancer belongs to a malignant tumor of the digestive tract, which mainly happens in the colon in the gastrointestinal tract of patients, especially at the junction of the sigmoid colon and rectum[1]. Its incidence is extremely high, ranking as high as the third in the ranking of gastrointestinal tumors[2]. Intestinal obstruction is a relatively common complication of colon cancer[3]. The main reason for intestinal obstruction in patients with colon cancer is that the intestinal cavity is usually narrow due to colon cancer, and the stool in the intestine is dry and hard, which leads to the passage of intestinal contents[4]. The early symptoms of acute intestinal obstruction are insidious and difficult to detect, and development of acute intestinal obstruction is rapid after onset, which is easy to lead to death[5]. At present, surgery is often used in the clinical therapy of colon cancer complicated with intestinal obstruction[6], but traditional laparotomy is not only easy to lead to large wounds, but also prone to more complications, which has adverse effects on the rapid recovery of patients[7]. Laparoscopic surgery is increasingly utilized in the treatment of colon cancer complicated by intestinal obstruction, owing to its benefits of reduced postoperative wound size, minimized intraoperative blood loss, fewer postoperative complications, and accelerated recovery times[8]. This study aimed to evaluate the clinical outcomes and prognosis associated with laparoscopic surgery in patients with colon cancer complicated by intestinal obstruction.

MATERIALS AND METHODS

General data

Clinical data from 100 patients diagnosed with colon cancer complicated by intestinal obstruction who underwent surgical treatment at our hospital between January 2020 and December 2022 were retrospectively analyzed. Patients were divided into two groups based on surgical approach: The control group (CG) and the observation group (OG), with 50 patients in each group. Inclusion criteria were: (1) Diagnosis of colon cancer with concurrent intestinal obstruction; and (2) No prior treatment before surgery. Exclusion criteria included: (1) Presence of malignant tumors at other sites; (2) Abnor-mal cardiac, hepatic, or renal function; (3) Prior open surgery; and (4) Intestinal perforation. Baseline characteristics showed no significant differences between the two groups ($P > 0.05$), indicating comparability.

Methods

Both groups underwent general anesthesia prior to surgery, and an artificial pneumoperitoneum with a pressure of approximately 15 mmHg was established. Surgical positioning varied according to the location of the tumor and the site of the intestinal obstruction.

The CG underwent a traditional laparotomy. A midline incision was made in the lower abdomen, progressing through successive layers of subcutaneous tissue. The tumor and obstruction sites were carefully examined to assess their size, location, and relation to surrounding tissues, guiding the selection of resection methods for both tumor and lymph nodes. Following resection, hemostasis was confirmed, and the abdominal cavity was irrigated. The incision was closed in layers, and a drainage tube was positioned. Postoperative management included routine anti-infection measures and fluid rehydration.

The OG received laparoscopic surgery. A puncture site was created bilaterally below the umbilicus, each incision measuring approximately 10 mm, allowing for laparoscopic access to the abdomen. Tumor and obstruction sites were visualized laparoscopically. Additional puncture sites were established bilaterally in the upper abdomen, each measuring approximately 5 mm for trocar insertion. The size, location, and adjacent structures of the tumor and obstruction were further assessed, allowing precise placement of primary and secondary operating ports. Through these, intestinal adhesions were lysed, and tumor along with lymph nodes were resected. The abdominal cavity was rinsed with normal saline, and incisions were sutured in layers. Postoperatively, patients received standard anti-infective and rehydration therapy.

Observation indicators

(1) Evaluation of clinical effects. Cure: After treatment, the patient's clinical symptoms and pathological tumor disappeared, X-ray examination showed no intestinal dilation in the abdomen, incision healing without complications; Improvement: The clinical symptoms were significantly improved, the lesion and tumor were reduced by more than half, and the abdominal intestinal obstruction was partially relieved by X-ray examination. Ineffective: Those who do not meet the above criteria or whose disease worsens. Total effective rate = cure rate + improvement rate; (2) Evaluation of surgical indicators, the operation time, intraoperative blood loss, recovery time of intestinal function, time of getting out of bed and hospital stay of patients were observed and recorded; (3) Pain score was evaluated using numerical rating scale (NRS). The total score was 0-10 points; (4) Inflammatory factors. 5 mL of fasting peripheral blood was gathered from patients before and 3 days after surgery in the morning, respectively. Serum was collected after centrifugation, and the serum levels of TNF-α, IL-6 s well as CRP were examined by help of double-antibody sandwich enzyme-linked immunosorbent assay; (5) The occurrence of complications including pulmonary infection, incision infection, intra-abdominal hemorrhage and anastomotic fistula in both groups was compared; (6) The postoperative quality of life score of the two groups was compared, including physical function, psychological state, social communication, as well as self-care ability, 25 points for each item, the total score of 0-100 points; (7) Postoperative intra-abdominal drainage volume, to compare the postoperative one day, three days, and total intra-abdominal drainage volume between two groups of patients; and (8) Prognostic indicators including postoperative tumor recurrence rate, tumor metastasis rate, survival rate within 1 year after surgery, and survival rate within 3 years after surgery.

Statistical analysis

This experiment was conducted with SPSS 22.0 statistical analysis software. The measurement data of normal distribution were exhibited as mean ± SD, and *t*-test was adopted for analysis. The count data were expressed as rate (%) and χ^2 test was performed between groups. $P < 0.05$ meant the difference was statistically significant.

RESULTS

Clinical effect in both groups

The study results indicated that, in the CG, 20 patients were classified as cured, 22 as improved, and 8 as ineffective, yielding a total effective rate of 84.00% (42 out of 50 patients). In the OG, 26 patients were classified as cured, 23 as improved, and 1 as ineffective, with a total effective rate of 98.00% (49 out of 50 patients). The effective rate in the OG was significantly higher than that in the CG ($P < 0.05$), as shown in Table 1 and Table 2.

Surgical indicators in both groups

The operation time, intraoperative blood loss, recovery time of intestinal function, time of getting out of bed and hospital stay of patients in the OG presented shorter relative to the CG, the difference is statistically significant ($P < 0.05$, Figure 1).

Degree of pain in both groups

No difference was seen in NRS score between 2 groups before surgery ($P < 0.05$). After surgery, the NRS score was declined in both groups, and that in the OG presented lower when comparing with the CG ($P < 0.05$, Figure 2).

Inflammatory response in both groups

There was no difference was seen in tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP) levels between CG and OG before surgery ($P < 0.05$). After surgery, TNF-α, IL-6 as well as CRP levels were increased in both groups, but those in the OG presented lower when comparing with the CG, the difference is statistically significant

Table 1 General data of patients in both groups, mean ± SD

Indicators		Control group (*n* = 50)	Observation group (*n* = 50)	*P* value
Gender (male/female)		30/20	29/21	> 0.05
Average age (year)		52.93 ± 8.35	53.06 ± 8.47	> 0.05
TNM stage	Stage I	20	21	> 0.05
	Stage II	25	24	
	Stage III	5	5	

Table 2 Clinical effect in both groups, *n* (%)

Groups	*n*	Cure	Improvement	Ineffective	Total effective rate
Control group	50	20	22	8	42 (84.00)
Observation group	50	26	23	1	49 (98.00)
χ^2					5.983
P value					< 0.05

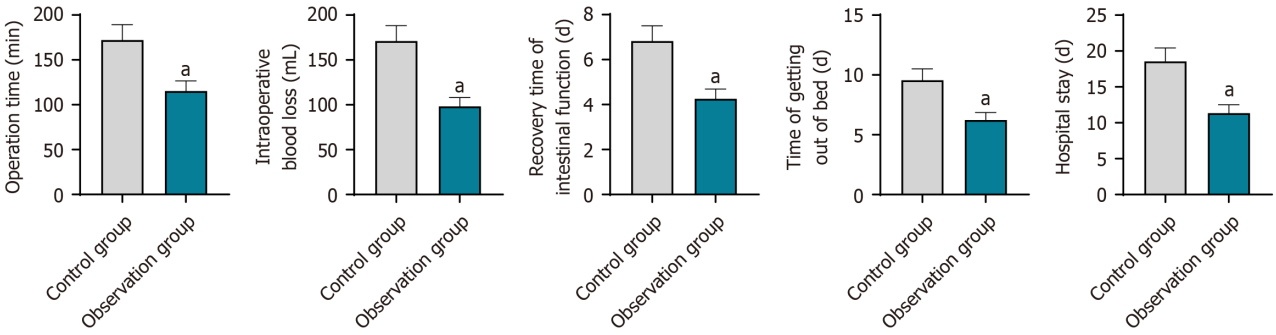

Figure 1 Surgical indicators in both groups. [a]*P* < 0.05.

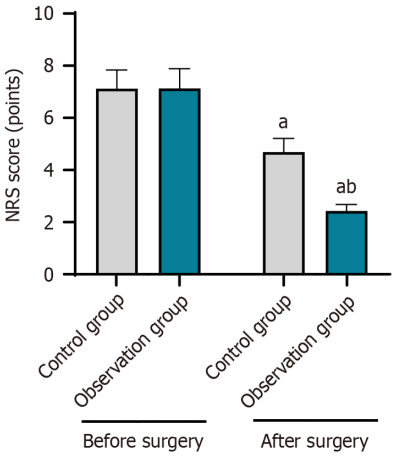

Figure 2 Degree of pain in both groups. [a]*P* < 0.05 *vs* before surgery; [b]*P* < 0.05 *vs* control group. NRS: Numerical rating scale.

(*P* < 0.05, Figure 3).

Occurrence of complications in both groups

The results of this study showed that there were 1, 0, 1, and 1 cases of pulmonary infection, incision infection, intra-abdominal bleeding, and anastomotic leakage respectively, the overall incidence of adverse reactions after surgery was 3 (6.00%) in OG. There were 3, 2, 3 and 3 cases of pulmonary infection, incision infection, intra-abdominal bleeding, and

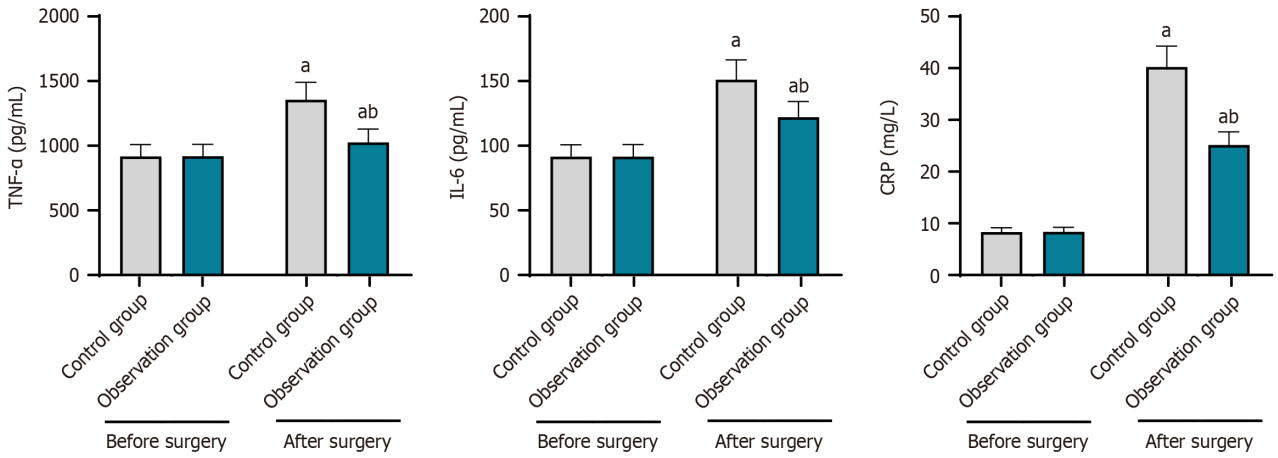

Figure 3 Inflammatory response in both groups. [a]*P* < 0.05 *vs* before surgery; [b]*P* < 0.05 *vs* control group. TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6; CRP: C-reactive protein.

anastomotic leakage respectively, and the overall incidence of adverse reactions after surgery was 11 (22.00%). Table 3 displayed that the occurrence of complications in the OG presented lower when comparing with the CG ($P < 0.05$).

Quality of life in both groups

After surgery, the quality of life scores including physical function, psychological state, social communication as well as self-care ability in the OG presented higher when comparing with the CG ($P < 0.05$, Figure 4).

Postoperative drainage volume

There was no significant difference in abdominal drainage volume and total drainage volume between the two groups of patients three days and seven days after surgery ($P > 0.05$) (Table 4).

The prognosis in both groups

The 1-year tumor recurrence rate, 1-year tumor metastasis rate, 1-year survival rate, and 3-year survival rate of the CG were 20% (10/50), 10% (5/50), 90% (45/50), and 64% (32/50), respectively. The OG had a 1-year tumor recurrence rate, tumor metastasis rate, 1-year survival rate, and 3-year survival rate of 14% (7/50), 6% (3/50), 92% (46/50), and 70% (35/50), respectively. There was no significant difference in the 1-year tumor recurrence rate, 1-year tumor metastasis rate, 1-year survival rate, and 3-year survival rate between the two groups ($P > 0.05$) (Table 5).

DISCUSSION

Intestinal obstruction is one of the most common clinical complications of colon cancer, the cause of which is closely related to postoperative infection and intestinal adhesion in patients with colon cancer[9]. The clinical symptoms are often manifested as abdominal distension, constipation and vomiting, *etc.*[10]. Because the early symptoms of intestinal obstruction are not easy to detect, and the development rate after the onset of the disease is fast, it possesses a great adverse influence on the survival, quality of life and postoperative recovery of patients[11].

At present, surgery is usually used in clinical therapy of colon cancer complicated with intestinal obstruction, and the curative effect is exact, the tumor can be removed in one time, and the obstruction can be removed in one time[12]. Traditional laparotomy is the main choice for the clinical therapy of colon cancer complicated with intestinal obstruction, which has good therapeutic effect and can effectively remove the tumor and relieve the intestinal obstruction of patients [13]. However, the traditional open surgery will leave a large wound and multiple postoperative complications, resulting in a slow postoperative recovery[14]. Therefore, in the therapy of colon cancer patients with intestinal obstruction, it is particularly important to adopt a surgical treatment with small postoperative wounds, fewer postoperative complications, and rapid postoperative recovery, which not only improves the survival rate of patients, but also promotes the quality of life of patients.

In recent years, minimally invasive surgery has been extensively applied in abdominal surgery, and laparoscopic surgery, as a kind of minimally invasive surgery, has been widely used in clinical treatment for its advantages of small postoperative wound, less intraoperative blood loss, fewer postoperative complications and quick postoperative recovery [15]. In treating colon cancer complicated with intestinal obstruction patients, laparoscopic surgery can observe the patient's abdominal cavity through the video probe[16]. At the same time, the magnification of laparoscopy can effectively ensure the surgical field of view, so that the patient's lesion area is fully and clearly exposed[17]. Moreover, laparoscopy has the advantage of multi-angle exploration, so that the positions that are not easily observed in traditional open surgery are also clearly exposed, which is convenient for doctors to carry out detailed and clear surgical operations [18]. In addition, laparoscopic surgery can also effectively decrease the operation time together with postoperative

Table 3 Occurrence of complications in both groups, *n* (%)

Groups	*n*	Pulmonary infection	Incision infection	Intra-abdominal hemorrhage	Anastomotic fistula	Total incidence rate
Observation group	50	1	0	1	1	3 (6.00)
Control group	50	3	2	3	3	11 (22.00)
χ^2						5.316
P value						< 0.05

Table 4 Postoperative drainage volume, mean ± SD

	Control group	Observation group	*t* value	*P* value
3-day drainage tube drainage volume (mL)	671.03 ± 228.52	670.21 ± 219.15	0.35	0.52
7-day drainage tube drainage volume (mL)	1220.95 ± 506.43	1224.85 ± 503.05	0.63	0.31
Total drainage tube drainage volume(mL)	1652.63 ± 520.15	1662.15± 521.83	0.54	0.37

Table 5 Occurrence of complications in both groups, *n* (%)

Groups	*n*	1-year tumor recurrence rate	1-year tumor metastasis rate	1-year survival rate	3-year survival rate
Observation group	50	17 (14)	3 (6)	46 (92)	35 (70)
Control group	50	10 (20)	5 (10)	45 (90)	32 (64)
χ^2		0.638	0.543	0.122	0.407
P value		0.424	0.461	0.727	0.523

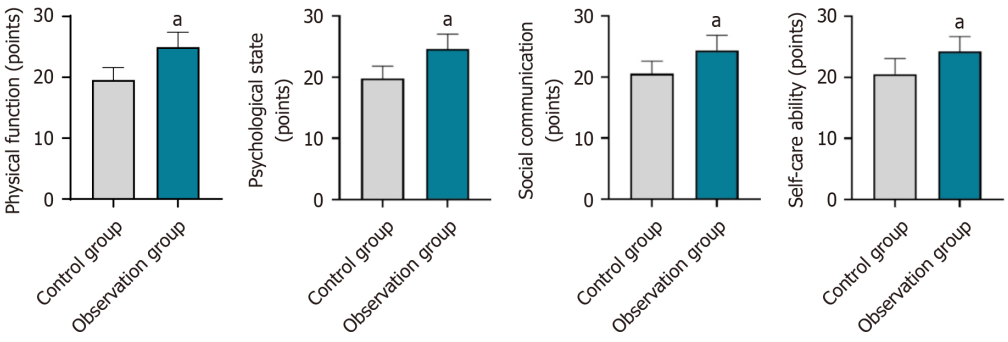

Figure 4 Quality of life in both groups. $^{a}P < 0.05$.

wounds, effectively decline the amount of intraoperative blood loss and postoperative complications, and speed up the postoperative recovery of patients[19].

Our study demonstrated that the overall clinical efficacy was greater in the OG compared to the CG. Patients in the OG experienced shorter operation times, reduced intraoperative blood loss, faster recovery of intestinal function, earlier mobilization, and reduced hospital stays compared to those in the CG. Both groups showed a reduction in NRS pain scores postoperatively; however, the OG reported significantly lower scores than the CG. These findings suggest that laparoscopic surgery may contribute to reduced hospital stays, lower intraoperative blood loss, decreased postoperative pain, enhanced clinical treatment efficiency, and accelerated rehabilitation for patients with colon cancer complicated by intestinal obstruction. This aligns with findings by Ruben Veldkamp *et al*[20], who reported that laparoscopic colectomy is associated with earlier bowel function recovery, reduced analgesic requirements, and shorter hospital stays compared to open colectomy.

During surgical trauma, patients would also activate the inflammatory response and promote the secretion of inflammatory factors[21]. TNF-α is a pro-inflammatory factor, which is secreted by mononuclear macrophages. IL-6 is an important cytokine, which can not only regulate immunity between cells, but also cooperate with other cytokines in the patient to transmit inflammatory response, which is one of the important indicators to evaluate the degree of surgical trauma in patients[22]. CRP is an important mediator of acute inflammation. When patients suffer from surgical trauma, its level will be significantly increased, which greatly improves the tissue repair ability of patients[23]. However,

literatures have found that CRP levels in patients is positively linked to the degree of surgical trauma[24]. Our study indicated that after surgery, TNF-α, IL-6 as well as CRP levels presented increased in both groups, but those in the OG presented lower when comparing with the CG, suggesting that the use of laparoscopic surgery could inhibit the inflammatory response in colon cancer complicated with intestinal obstruction patients. Consistently, it has been reported that the inflammatory response presents lower in laparoscopic rectal surgery when comparing with conventional open surgery[25].The systemic inflammatory response after major surgery is initially the result of a highly conservative innate immune response. Depending on the surgical environment, it varies greatly and is directly proportional to the degree of surgical injury[26]. The relevant molecular patterns are key molecular ligands that trigger inflammatory and immune responses after surgical injury. At the site of injury, DAMPs such as heat shock proteins, S100 proteins, high mobility group B proteins, nucleic acids, DNA, and adenosine triphosphate bind to pattern recognition receptors and send signals to innate immune cells[27]. The activation of pattern recognition receptors induces multiple downstream signaling pathways, leading to the activation of NF-κB, activator protein 1, and interferon regulatory factors[28]. It can also drive the production and release of pro-inflammatory cytokines and chemokines (such as IL-6, TNF-α, IL-1b, IL-8, IL-12, type 1 interferon), leukotrienes (such as leukotriene B4), and DAMPs (such as HMGB1), leading to an increase in the production of neutrophils and monocytes, which are recruited to the site of injury[29,30]. It can also promote NK cell activation, release of reactive oxygen species, increase phagocytosis, and alter endothelial permeability. Inflammation immune response is always balanced because immune suppression and immune activation begin simultaneously. The level of IL-6 is closely related to the severity of injury and the synthesis and release of postoperative CRP[31,32]. However, after binding to IL-1b and TNF-α, it can also stimulate the hypothalamic pituitary adrenal axis, increase cortisol secretion, and affect glucocorticoid mediated immune regulation[33,34]. In addition, when IL-6 reacts with glucocorticoids and anti-inflammatory cytokines (such as IL-4), it can promote the transformation of naive T cells into immunosuppressive type 2 (Th2) phenotype, thereby producing anti-inflammatory cytokines (IL-4, IL-10, IL-13) to suppress cellular immunity. IL-6 can also induce macrophages to release prostaglandin E2, which is a potent immunosuppressant that negatively regulates the function of monocytes, macrophages, and T cells[35,36]. In summary, these functions demonstrate the dual role of IL-6, which serves as a pro-inflammatory cytokine to drive the initial host response, while also promoting immune regulation and inhibition.

The prognosis of general colon cancer patients is closely related to the timing of colon cancer staging at the time of diagnosis. In addition, the pathological type of colon cancer, the location of the lesion, the level of surgery, and the postoperative adjuvant treatment also directly affect the prognosis of colon cancer patients[36,37]. The prognosis of different stages of colon cancer during surgery is significantly different. The five-year survival rate of stage I colon cancer after surgery can reach over 90%, while the five-year survival rate of stage II colon cancer may only be around 70%[38-40]. The five-year survival rate of stage III colon cancer patients after surgery is only about 40%-50%. If stage IV colon cancer is diagnosed with metastasis to distant organs such as the liver and lungs, the prognosis of patients will be even worse, and the survival period will often be significantly shortened[41]. The results of this study show that there was no significant difference in the 1-year tumor recurrence rate, 1-year tumor metastasis rate, 1-year survival rate, and 3-year survival rate between the two groups ($P > 0.05$). In the pathological grading of colon cancer, the prognosis of poorly differentiated colon cancer is often much worse than that of highly differentiated colon cancer[42]. Patients who can undergo radical surgical resection during surgery often have a better prognosis than those who cannot undergo radical surgical resection. For some patients who require postoperative adjuvant chemotherapy based on pathological reports, if they complete it on time, their survival will be significantly prolonged, longer than those who require postoperative adjuvant chemotherapy without treatment[43]. So the most important thing to improve the prognosis of colon cancer patients is to be able to detect and diagnose early, and provide active treatment early, thereby prolonging the patient's survival time.

CONCLUSION

In addition, our study indicated that the occurrence of complications in the OG presented lower when comparing with the CG, and the quality of life scores including physical function, psychological state, social communication as well as self-care ability in the OG presented higher when comparing with the CG. All above outcomes indicated that the application of laparoscopic surgery could reduce the complications and promote the quality of life of colon cancer complicated with intestinal obstruction patients, which was in line with previous studies[44,45]. In conclusion, laparoscopic surgery has a significant effect in treating colon cancer complicated with intestinal obstruction patients, which can effectively lessen the pain of patients, reduce the inflammatory indicators of patients, decline the postoperative complications of patients, as well as promote the quality of life of patients.

FOOTNOTES

Author contributions: Wu PH contributed to the study conception, data collection, and analysis, as well as drafting the manuscript; Ta ZQ supervised the study design, provided critical revisions to the manuscript, and ensured the integrity of the data and the accuracy of the analysis. Both authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy of microwave ablation *vs* laparoscopic hepatectomy for primary small liver cancer: A comparative study

Huan-Song Li, Xuan-Feng Zhang, Jun Fu, Bo Yuan

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Abstract

BACKGROUND

In-depth comparative investigations in terms of clinical efficacies of liver tumor microwave ablation (MWA) and laparoscopic hepatectomy (LH), which are both important treatment modalities for liver neoplasms, have been limited in patients diagnosed with primary small liver cancer (PSLC).

AIM

To compare and analyze the clinical efficacy of liver tumor MWA and LH for PSLC.

METHODS

This study retrospectively analyzed the medical records of 123 patients with PSLC admitted to Xuzhou Central Hospital from January 2015 to November 2022 and categorized them based on treatment modalities into the LH and MWA groups. The LH group, consisting of 61 cases, received LH, and the MWA group, which included 62 cases, underwent liver tumor MWA. Basic data and various perioperative indicators were compared between the two groups, including changes in liver function indicators [alanine aminotransferase (ALT), glutamic aminotransferase (AST), and total bilirubin (TBIL)] pre- and post-treatment, and efficacy and postoperative complications were analyzed.

RESULTS

No statistically significant difference was observed between the two groups in terms of age, gender, tumor diameter, liver function Child-Pugh classification and number of tumors, body mass index, and educational status ($P > 0.05$). The overall effective rate was higher in the MWA group than in the LH group (98.39% *vs*

88.52%) (χ^2 = 4.918, P = 0.027). The MWA group exhibited less operation time, intraoperative bleeding, defecation time, and hospital stay than the LH group (P < 0.05). No difference was found in liver function indicators between the two groups pre-treatment (P > 0.05), and ALT, AST, and TBIL levels decreased in both groups post-treatment, with the MWA group demonstrating lower levels (P < 0.05). The MWA and LH groups exhibited postoperative complication rates of 4.84% and 19.67%, respectively, with statistically significant differences between the two groups (P = 0.012, χ^2 = 6.318).

CONCLUSION

MWA is more effective in treating PSLC, and it promotes faster postoperative recovery for patients, and more security improves liver function and reduces postoperative complications compared to LH.

Key Words: Microwave ablation of liver tumors; Laparoscopic hepatectomy; Primary small liver cancer; Clinical outcome

Core Tip: This study primarily aimed to comparatively analyze the clinical effectiveness of liver tumor microwave ablation (MWA) and laparoscopic hepatectomy (LH) in treating primary small liver cancer (PSLC). We conducted a comparative analysis of the two intervention methods from multiple perspectives, including various perioperative indicators, changes in liver function indicators pre- and post-treatment, curative effects, and postoperative complications. This study confirmed that MWA demonstrated better curative effects than LH in PSLC treatment, with a reduced intraoperative blood loss level, shorter surgical procedure and hospitalization durations, rapid recovery facilitation, liver function improvement, postoperative complication reduction, and a high safety level. Therefore, selecting the appropriate surgical method is the key to achieving better clinical outcomes. Our analysis provides more reliable clinical references and options for future PSLC treatment.

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INTRODUCTION

Primary small liver cancer (PSLC), one of the most prevalent malignant tumors globally[1,2], is a digestive system malignancy characterized by high morbidity and mortality rates. According to statistics, over 90% of primary liver cancers were hepatocellular carcinomas[3], and the rest were cholangiocellular and mixed-type hepatocellular carcinomas. Hepatocellular carcinoma was categorized based on morphological characteristics into nodular, massive, and diffuse, and according to tumor size as microscopic (diameter ≤ 2 cm), PSLC (> 2 cm, ≤ 5 cm), large (> 5 cm, ≤ 10 cm), and giant hepatocellular carcinomas (> 10 cm). One of the small liver cancers was known as early-stage liver cancer or subclinical liver cancer, with generally no obvious clinical signs and symptoms. PSLC is generally characterized by pain in the liver area, weakness, lack of appetite, wasting, and fever[4,5]. It is potentially correlated with viral hepatitis, aflatoxin, metabolic and genetic determinants, chronic alcohol ingestion, smoking, and other relevant factors[6]. The proportion of PSLC in all liver cancers is increasing annually as awareness of risk factors for primary liver cancer and health screening increases and the detection rate of small liver cancers rises due to medicine development[7]. For the treatment of primary liver cancer, the major clinical approaches include surgical resection, ablation, liver transplantation, and drug therapy[8]. The standard treatment options for PSLC were laparoscopic surgical resection and microwave ablation (MWA) of liver tumors, which represent surgical and ablative procedures, respectively. The treatment protocol that effectively manages the disease while minimizing patient harm was individually determined, considering the specific circumstances of each patient.

The etiology and pathogenesis of PSLC are currently undetermined[9]. Academic research indicated that early detection and treatment effectively save the lives of patients with PSLC[10-12]. One study[13] revealed laparoscopic hepatectomy (LH) to be less damaging to patients' liver function, demonstrates higher liver function reserve capacity, is less invasive, causes less intraoperative bleeding, and exhibits a lower incidence of postoperative complications than open hepatectomy. The range of inactivated tissues is expanding with the continuous improvement of ablation techniques, thereby increasing definitive treatment results[14,15]. MWA is the use of physically generated high heat to coagulate and inactivate tumor tissue in the body[16,17], prompting the body to decompose, remove, or mechanize necrotic tissue, thereby destroying the lesion for eradication. MWA is less traumatic for patients and exhibits the characteristics of simple operation, quick recovery, safety, and efficiency[18]. Furthermore, it does not require tumor removal, which indicates the presence of a variety of minimally invasive methods available and a wealth of treatment opportunities and options for patients with liver cancer[19]. Moreover, it cures patients who cannot undergo surgical treatment. MWA, LH, and other surgical modalities were gaining clinical attention as one of the important treatment methods for liver tumors. A wide

range of medical practitioners acknowledged its advantages and disadvantages.

However, studies comparing MWA with LH were scarce. This study aims to investigate the clinical efficacy of MWA and LH in PSLC treatment.

MATERIALS AND METHODS

Subjects

This study retrospectively analyzes the medical records of 123 patients with PSLC admitted to Xuzhou Central Hospital from January 2015 to November 2022, categorized based on treatment modality into the LH (61 cases) and MWA groups (62 cases).

Diagnostic criteria of PSLC

Hepatocellular carcinoma confirmed by liver puncture histopathology or postoperative pathology; a single cancer foci of ≤ 3 cm in diameter; liver function Child-Pugh grades A or B[20].

Inclusion criteria

Age of > 18 years and ≤ 69 years; normal preoperative coagulation and other indicators; no extrahepatic transfer or other surgical, chemotherapeutic, or anti-tumor treatments.

Exclusion criteria

Patients with surgical contraindications; incomplete case information; cardiac, pulmonary, renal, and other vital organ insufficiency; pregnant and lactating women. The basic information of the two groups of patients.

Shedding or rejection criteria

Lost to follow-up post-discharge; automatically discharged from hospital during treatment; serious complications occurring during hospitalization (malignant arrhythmia, myocardial infarction, cardiac arrest, severe decline in muscle strength, *etc.*); rejecting the experimenter midway.

Criteria for loss of follow-up

Those who were actively hospitalized and refused to be followed up by telephone, or those who were unreachable during the follow-up period due to force majeure factors.

Treatment process

The LH group received LH, with the operation as follows. The patient is positioned supine. A 1-cm sub-umbilical incision was created after general anesthesia, and pneumoperitoneum was established by puncture of pneumoperitoneum needle. A 1-cm Trocar was placed *via* this puncture, and a laparoscopic lens was placed to explore for abdominal fluid, tumor site, size, and number, cases with a liver texture, *etc.*, that was compatible with surgical resection. The position of the other operating trocar was identified based on the specific tumor location. The corresponding lesion area of the liver was resected with the help of an ultrasonic knife and bipolar electrocoagulation, and the resection line was identified at 2 cm from the surface of the tumor with an electric knife. The resection line was gradually cut through the liver tissue from superficial to deep and from anterior to posterior for complete resection of the liver tumor. The large vessels and corresponding bile ducts were clamped closed with a titanium clip during excision, and hemostasis was achieved through electrocoagulation. The tumor was placed in a specimen bag, and the specimen was removed from the bag after dilatation through the sub-umbilical observation hole.

The MWA group underwent liver tumor MWA as follows. The preceding steps were performed in the supine position, under general anesthesia, with pneumoperitoneum establishment and laparoscopic lens exploration, as previously in the LH group. A thermal isolation zone was established and the MWA needle was placed in the center of the tumor under the lumpectomy after accurate exploration of the tumor location under the guidance of the lumpectomy ultrasound probe. The appropriate radiofrequency voltage and time were then set and the ablation treatment was initiated after determination. The ablation protocol was selected based on the tumor size. A one- or two-point MWA was utilized for lesions of ≤ 2 cm in diameter, and a multi-point MWA was employed for lesions of > 2 cm in diameter. The ablation output was 60 W, and each ablation cycle lasted 5 minutes. The coagulation mode was changed and the needle tract was cauterized to prevent bleeding from the needle tract and to end the procedure if the ultrasound showed complete tumor ablation post-treatment. Ablation treatment was continued if tumor ablation was incomplete, and the tumor exhibited hyperechoic changes on ultrasound post-procedure, with inactivated tissue beyond the preoperative tumor margins. The procedure was completed with the choice of whether to perform a hilar block or hemihepatic blood flow block, based on tumor location in both groups.

Observation methods

Efficacy criteria[21] were identified based on the patient's peritoneal fluid into complete remission (CR), which is the complete disappearance of ascites maintained for more than one month; partial remission (PR), with over 50% reduction in ascites; stabilizing disease (SD), with no significant change in ascites and less than 50% reduction from pre-treatment; progressive disease, with a > 25% increase in ascites from pre-treatment. Total effective rate = (CR + PR + SD) / total

number of cases × 100%. The extraction time, intraoperative bleeding, defecation, and length of hospital stay were recorded for both groups. Liver function indexes pre- and post-treatment were taken from an automatic biochemical analyzer, consisting of alanine aminotransferase (ALT), glutamic aminotransferase (AST), and total bilirubin (TBIL). Postoperative complications were documented in both groups, including nausea and vomiting, lung infection, incisional infection, and abdominal bleeding. All patients were followed up from December 1, 2016, to March 30, 2023.

Statistical analysis

The measurement data (including age and tumor diameter, body mass index, operation time, intraoperative bleeding, defecation time, length of hospital stay, and liver function indicators) were presented as mean ± SD using the *t*-test. The count data (gender, educational status, liver function Child-Pugh classification, number of tumors, efficacy, and postoperative complications) were expressed as rates and percentages (%) using χ^2 tests. The test level was $\alpha = 0.05$. Statistical Package for the Social Sciences version 23.0 was used for analysis.

RESULTS

Comparison of basic information between the two groups of patients

No statistically significant difference was found between the two groups in terms of age, gender, tumor diameter, liver function Child-Pugh classification and the number of tumors, body mass index, and educational status ($P > 0.05$) (Table 1).

Comparison of the efficacy of the two groups of patients

The total effective rate after treatment was 98.39% in the MWA group, which was significantly higher than in the LH group at 88.52%, with a statistically significant difference ($P < 0.05$) (Table 2).

Comparison of perioperative indicators between the two groups of patients

The operative time, intraoperative bleeding, defecation time, and hospital stay were less in the MWA group than in the LH group ($P < 0.05$) (Figure 1).

Comparison of liver function indicators pre- and post-treatment between the two groups

No difference was observed in the comparison of liver function indexes between the two groups pre-treatment ($P > 0.05$), and ALT, AST, and TBIL levels decreased in both groups post-treatment, which were lower in the MWA group than in the LH group ($P < 0.05$) (Figure 2).

Comparison of postoperative complications between the two groups

The incidence of postoperative complications in the MWA group compared to the LH group (4.84% *vs* 19.67%) was statistically significant ($P = 0.012$, $\chi^2 = 6.318$), tolerable, and promptly managed without affecting the normal treatment course and symptom relief (Table 3).

DISCUSSION

Research reveals that[22] laparoscopic MWA combined with hepatic artery chemoembolization is a safe and effective treatment option for early-stage hepatocellular carcinoma, with good recent results, prolonged survival, and low incidence of serious adverse events. This study revealed that MWA demonstrated a higher overall efficiency than LH (98.39% *vs* 88.52%), indicating that MWA is more effective than laparoscopic liver resection for patients with PSLC. This may be attributed to the application of an ablation needle in the MWA procedure. The ablation needle is accurately inserted into the tumor through the liver tissue under ultrasonography guidance. Subsequently, the electrode needle of the ablation device is used to generate heat within the tumor tissue utilizing high-frequency alternating current, thereby achieving the ablation effect. Tumor tissues demonstrate relatively poor heat tolerance. Coagulative inactivation is induced within the tumor tissue and the adjacent parenchymal tissue once the local temperature exceeds 50°C. Irreversible impairment of tissue cells occurs when the temperature surpasses 60°C. Moreover, the increased temperature generated by the tissue can disrupt the blood vessels that supply the tumor and the surrounding tissues. Tumor tissue necrosis becomes more comprehensive as a consequence of nutrient deprivation, which consequently diminishes the probability of intrahepatic metastasis of the tumor[23,24]. Operative time, intraoperative bleeding, defecation, and hospital stay were less in the MWA group than in the LH group, indicating that MWA promotes early recovery and is more minimally invasive for patients with small liver cancers. Liver function indicators reflect liver damage in a timelier manner. Notably, ALT, AST, and TBIL hold considerable significance. High ALT, AST, and TBIL levels are closely associated with liver damage in the body. Effective treatment interventions decrease the levels of abnormally increased liver function indices[25]. ALT, AST, and TBIL levels were lower in the treated group than in the LH group post-treatment because MWA causes coagulation and necrosis of the tumor and local liver tissue, resulting in transient impairment of liver function, decrease in ALT, AST, and TBIL levels post-treatment, and a gradual return to normal liver function due to complete absorption of necrotic tissue[26]. MWA is more convenient, less damaging to liver function, and can be repeated multiple times for single hepatocellular carcinoma of ≤ 5 cm in diameter[27]. The incidences of post-

Table 1 Comparison of basic information between the two groups of patients

Group	LH group (*n* = 61)	MWA group (*n* = 62)	t/χ^2	*P* value
Age (years)	65.27 ± 16.08	66.18 ± 16.24	0.312	0.755
Gender (M/F)	34/27	33/29	0.078	0.780
Tumour diameter (cm)	4.53 ± 1.46	4.48 ± 1.43	0.192	0.848
Liver function Child-Pugh classification (A/B)	42/19	44/18	0.065	0.798
Number of tumours (single/multiple)	47/14	46/16	0.136	0.712
Body mass index (kg/m^2)	23.16 ± 4.75	23.23 ± 4.84	0.081	0.936
Education status (junior high school and below/high school and above)	39/22	37/25	0.236	0.627

LH: Laparoscopic hepatectomy; MWA: Microwave ablation.

Table 2 Comparison of the efficacy of the two groups of patients, *n* (%)

Group	Number of examples	CR	PR	SD	PD	Total efficiency
LH group	61	24 (39.34)	17 (27.87)	13 (21.31)	7 (11.48)	54 (88.52)
MWA group	62	39 (62.90)	16 (25.81)	6 (9.68)	1 (1.61)	61 (98.39)
χ^2						4.918
P value						0.027

CR: Complete remission; PR: Partial remission; SD: Stabilizing disease; PD: Progressive disease; LH: Laparoscopic hepatectomy; MWA: Microwave ablation.

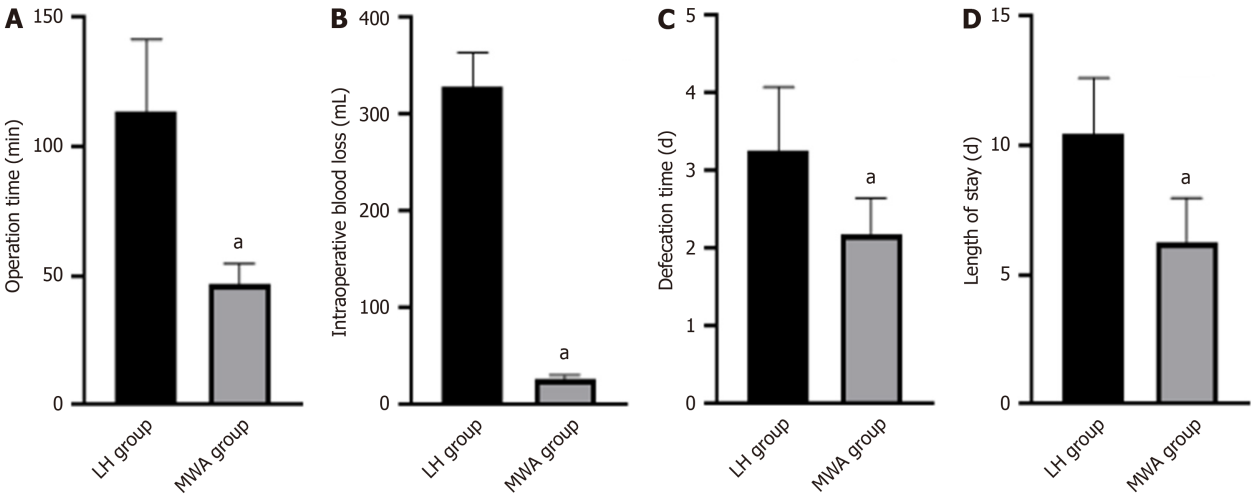

Figure 1 Comparison of perioperative indicators between the two groups of patients. Indicates comparison with laparoscopic hepatectomy group. A: The duration of surgery; B: The amount of intraoperative bleeding; C: The amount of intraoperative fluids; D: The length of hospital stay. $^aP < 0.05$. LH: Laparoscopic hepatectomy; MWA: Microwave ablation.

operative complications were 4.84% and 19.67% in the MWA and LH groups, respectively, with a statistically significant difference between the two groups. This indicates that MWA is a physical thermal ablation technique, with the thermal effect inducing tumor necrosis, thereby causing the death of tumor cells for therapeutic purposes. It exhibits a quick recovery, is less invasive, and demonstrates a high safety profile.

CONCLUSION

In conclusion, compared with LH, MWA of PSLC is more effective, with low intraoperative bleeding, shorter operation

Table 3 Comparison of post-operative complications between the two groups of patients, *n* (%)

Group	Number of examples	Post-operative complications				Total incidence
		Nausea and vomiting	Lung infections	Infection of the incision	Abdominal bleeding	
LH group	61	6 (9.84)	3 (4.92)	2 (3.28)	1 (1.64)	12 (19.67)
MWA group	62	2 (3.23)	1 (1.61)	0 (0.00)	0 (0.00)	3 (4.84)
χ^2						6.318
P value						0.012

LH: Laparoscopic hepatectomy; MWA: Microwave ablation.

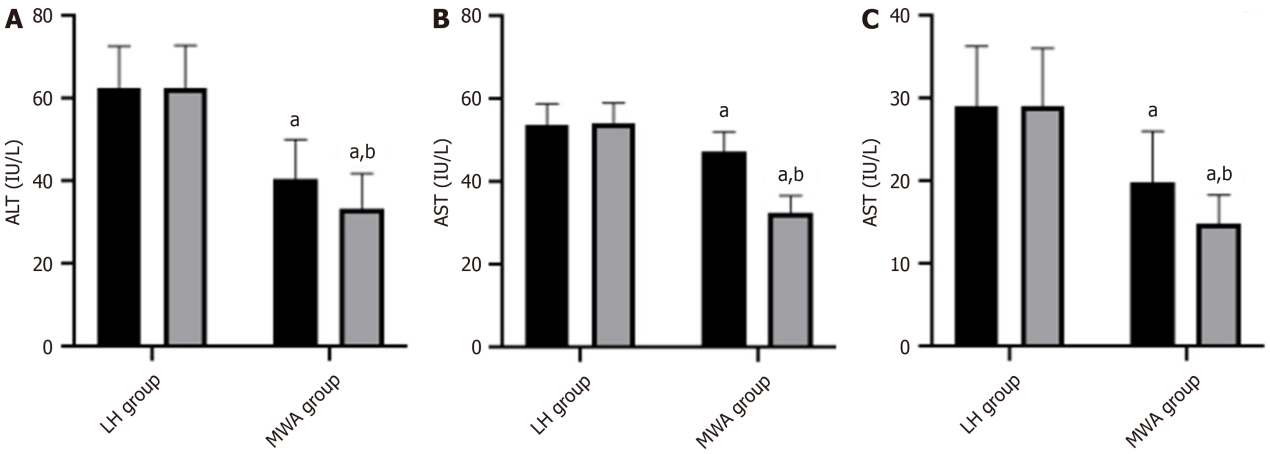

Figure 2 Comparison of liver function indicators before and after treatment between the two groups. A: Alanine aminotransferase levels; B: Glutamic aminotransferase levels; C: Total bilirubin levels. [a]*P* < 0.05 *vs* the same group before treatment; [b]*P* < 0.05 *vs* the laparoscopic hepatectomy group after treatment. ALT: Alanine aminotransferase; AST: Glutamic aminotransferase; LH: Laparoscopic hepatectomy; MWA: Microwave ablation.

and hospital stay, rapid recovery, improved liver function, reduced postoperative complications, and high safety; thus, selecting the appropriate procedure is the key to achieving better clinical results.

FOOTNOTES

Author contributions: Li HS and Zhang XF designed the research and wrote the first manuscript; Li HS, Zhang XF, Fu J and Yuan B contributed to conceiving the research and analyzing data, conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript. Li HS and Zhang XF contributed equally to this work as co-first authors. Both Fu J and Yuan B have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Yuan B conceptualized, designed, and supervised the whole process of the project. Fu J searched the literature, revised and submitted the early version of the manuscript. Fu J and Yuan B was instrumental and responsible for data re-analysis and re-interpretation, figure plotting, comprehensive literature search, preparation and submission of the current version of the manuscript. This collaboration between Fu J and Yuan B is crucial for the publication of this manuscript and other manuscripts still in preparation.

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ORIGINAL ARTICLE

Retrospective Study

High cellular prion protein expression in cholangiocarcinoma: A marker for early postoperative recurrence and unfavorable prognosis

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Abstract

BACKGROUND

The cellular prion protein (PrP^C), traditionally associated with neurodegenerative disorders, plays an important role in cancer progression and metastasis by inhibiting apoptosis.

AIM

To investigate the influence of PrP^C expression in cholangiocarcinoma (CCA) on patient outcomes following surgical resection.

METHODS

Patients who underwent curative surgical resection for either intrahepatic or hilar

CCA were enrolled in this retrospective study. Based on the immunohistochemical staining results of the surgical specimens, patients were categorized into two groups: The low PrP^C group (negative or 1+) and the high PrP^C group (2+ or 3+). Survival analyses, including overall survival and recurrence-free survival, were conducted using the Kaplan-Meier method and compared using the log-rank test.

RESULTS

In total, seventy-six patients diagnosed with CCA (39 with intrahepatic and 37 with hilar CCA) underwent curative hepatectomy from January 2011 to November 2021. Among these patients, 38 (50%) demonstrated high PrP^C expression, whereas the remaining 38 (50%) showed low expression of PrP^C. During a median follow-up period of 31.2 months (range: 1 to 137 months), the high PrP^C group had a significantly shorter median overall survival than the low PrP^C group (40.4 months *vs* 137.9 months, respectively; $P = 0.041$). Moreover, the high PrP^C group had a significantly shorter median recurrence-free survival than the low PrP^C group (13.3 months *vs* 23.8 months, respectively; $P = 0.026$).

CONCLUSION

PrP^C expression is significantly associated with early recurrence and decreased survival period in CCA patients following surgical resection. Thus, PrP^C may be used as a prognostic factor in treatment planning.

Key Words: Cholangiocarcinoma; Cellular prion protein; Liver neoplasms; Prognosis; Recurrence; Survival

Core Tip: High cellular prion protein (PrP^C) expression is significantly associated with early recurrence and decreased survival period in cholangiocarcinoma patients following surgical resection. PrPC expression serves as an independent prognostic factor for overall survival and recurrence-free survival. These findings suggest that PrPC could be a valuable prognostic biomarker following curative surgery.

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INTRODUCTION

Cholangiocarcinoma (CCA) arises from the epithelial cells lining the bile duct and ranks as the second most common primary liver cancer, following hepatocellular carcinoma[1]. CCA is anatomically classified into three subtypes: Intrahepatic, hilar, and distal CCA[2,3]. The global incidence of CCA is increasing, especially intrahepatic CCA, which is growing more rapidly than extrahepatic CCA[4-6]. Surgical resection remains the only curative treatment for CCA; however, only 35% of patients are considered suitable for curative resection at the time of diagnosis[7,8]. CCA has a dismal prognosis, with a five-year survival rate of less than 20%[6,9]. Even with standard chemotherapy (gemcitabine plus cisplatin), the median survival period for patients with advanced, unresectable CCA does not exceed 12 months[10]. Molecular genetic profiling of tumors and targeted therapies are emerging as important areas of research[11,12]. Despite these ongoing research efforts, the development of personalized chemotherapeutic agents is urgently needed, and the identification of novel prognostic biomarkers plays a critical role in next-generation CCA treatment.

The prion protein is a cell surface glycoprotein predominantly expressed in the central and peripheral nervous systems [13]. Prion proteins have two isoforms: The cellular prion protein (PrP^C) and the scrapie prion protein (PrP^{SC})[14]. Misfolding of PrP^C into PrP^{SC} can lead to fatal neurodegenerative disorders[15]. PrP^C plays an important role in the nervous and immune systems, influencing cell proliferation, differentiation, survival, and programmed cell death[16,17]. PrP^C is emerging as a potential target for chemotherapy, given its implicated involvement in tumor growth, metastasis, resistance to chemotherapy-induced cell death, and overall cancer progression across different cancer types[18,19]. However, the role of PrP^C expression in CCA remains unknown. In this study, we aim to investigate two questions: (1) The expression of PrP^C in CCA; and (2) The effects of PrP^C on long-term prognosis such as recurrence and survival following surgical resection.

MATERIALS AND METHODS

Study population

This retrospective study enrolled patients who underwent curative surgical resection for intrahepatic and hilar CCA at Hallym University Sacred Heart Hospital (Anyang, Republic of Korea) between January 2011 and November 2021. The inclusion criteria were as follows: (1) Adults aged 18 years or older; (2) Those who underwent radical resection for CCA; and (3) Histologically confirmed adenocarcinoma in surgical specimens. Exclusion criteria were as follows: (1) A history of being diagnosed with cancer other than primary CCA; (2) The presence of malignant ascites, peritoneal metastasis, or distant metastasis at diagnosis; (3) Prior neoadjuvant chemotherapy or chemoradiation therapy; (4) Uncontrolled infections, diabetes mellitus, hypertension, ischemic heart disease, or myocardial infarction within the last 6 months; and (5) Neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease.

After surgery, patients were monitored every three months for the first year and then every six months thereafter. Postoperative tumor recurrence evaluation included imaging tests, such as computed tomography or magnetic resonance imaging, and blood tests, including serum carbohydrate antigen 19-9 (CA19-9). If tumor recurrence was detected, appropriate treatment was administered. Data on demographics, radiologic and pathologic characteristics (tumor size, location, number of metastatic lymph nodes, resection margin, differentiation), blood tests (CA19-9 and carcinoembryonic antigen), along with survival and recurrence information, were retrospectively collected from electronic medical records. Tumor stages were assessed according to the American Joint Committee on Cancer staging system, eighth edition[20].

Immunohistochemical staining of surgical specimens using tissue microarrays

Tissue microarrays (TMAs) utilized a 2 mm tissue core from the designated region, which was subsequently re-embedded. Each sample was meticulously arranged in duplicate to minimize tissue loss. These TMA blocks were subsequently sliced into 4 μm thick sections, which were used for immunohistochemical staining. Prior to staining, TMA sections underwent deparaffinization with xylene and hydration through a graded ethanol series. Following established protocols, they were treated with a peroxidase-blocking solution (Dako, Copenhagen, Denmark) for 10 minutes to inhibit endogenous peroxidase activity. After blocking with a protein solution (Dako) for 60 minutes at room temperature, the sections were incubated with a diluted rabbit polyclonal antibody against PrP^C (8H4; Sigma-Aldrich, St. Louis, MO, United States). Detection was carried out following the primary antibody incubation, using the Dako EnVision Detection System kit (Dako), in accordance with the manufacturer's guidelines.

Evaluation of immunostainings

The TMA slides were analyzed to determine the proportion of tumor cells with positive PrP^C staining in their nuclei. An expert pancreaticobiliary pathologist (Cho YA) without any knowledge of the patients' personal or clinical data evaluated the PrP^C stainings. Immunoreactivity was assessed based on the histochemical scoring (H-score) system. The H-score was calculated by a semi-quantitative assessment of both the intensity of staining (graded as: 0, no evidence of staining; 1+, weak staining; 2+, moderate staining; or 3+, strong staining, using adjacent normal mucosa as the median) and the percentage of positive cells. Expression levels of each component were classified into low PrP^C or high PrP^C groups based on the median value of the H-score (Figure 1).

Endpoints

Overall survival (OS) and recurrence-free survival (RFS) were compared between the two groups. OS was calculated from the date of surgery to either the date of death or the last follow-up. RFS was defined as the time from the date of surgery to recurrence or death from any cause.

Statistical analysis

Continuous variables are presented as means ± SD, whereas categorical variables are presented as frequencies and proportions. Categorical data were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Continuous data were analyzed using Student's *t*-test. Survival analyses for both RFS and OS were conducted using Kaplan-Meier curves, and differences in survival were tested using the log-rank test. Multivariate analyses for recurrence and survival were conducted using the Cox proportional hazards regression model. Variables with a P value < 0.1 in univariate analysis were included in the multivariate Cox regression model. To ensure the stability of the model, the ratio of events to independent variables was maintained at a minimum of 10 events per variable. Statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Chicago, IL, United States) and R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

Table 1 summarizes the demographic and clinical characteristics of the patients. The study included seventy-six patients who underwent surgical resection for CCA. Among these patients, 38 (50%) demonstrated high PrP^C expression, whereas the other 38 (50%) showed low expression of PrP^C. The median age was 66.7 years, with most patients being men (64.5%). Nearly half of the study population had intrahepatic CCA (48.7%), whereas all other patients had hilar CCA (51.3%). All patients underwent curative-intent hepatectomy. The median tumor size was 4.7 ± 2.8 cm, and 44.7% of patients had

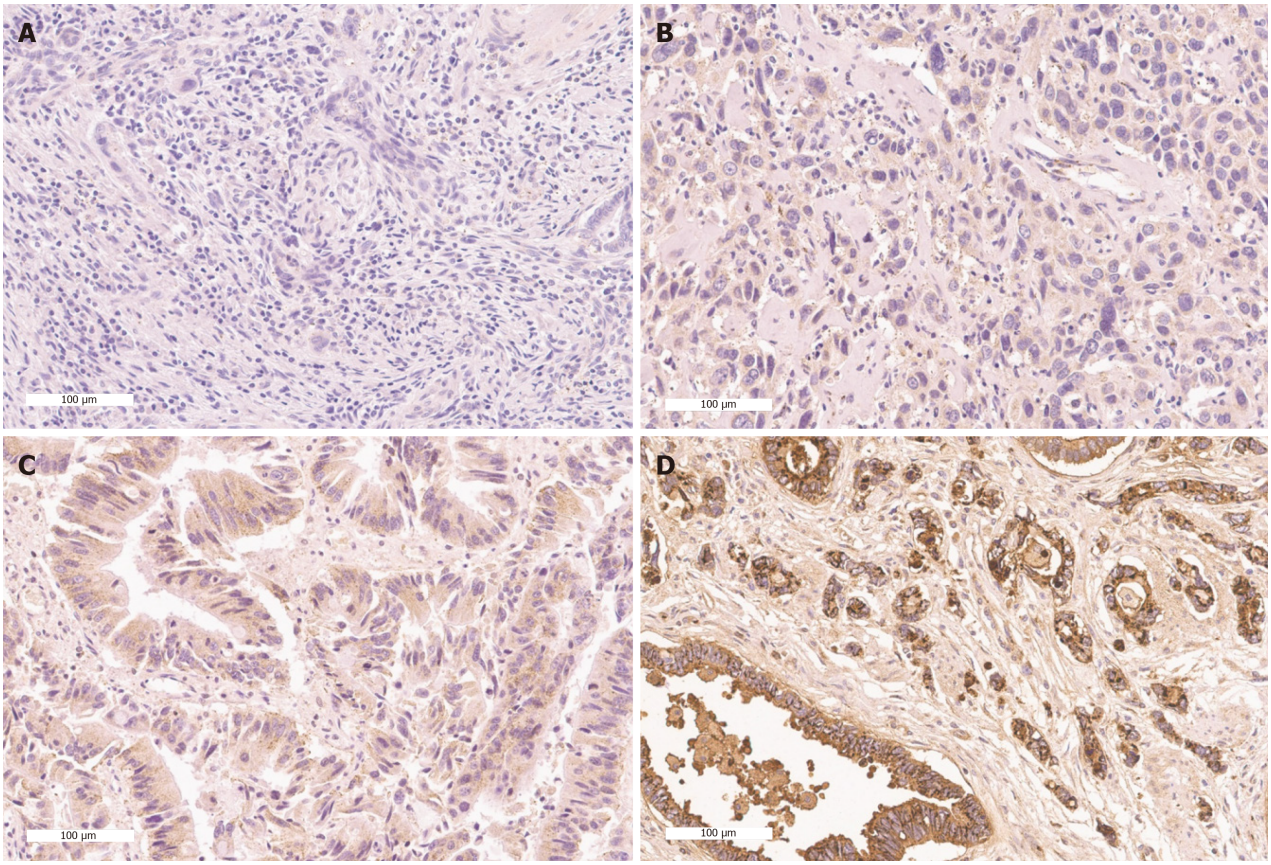

Figure 1 Representative figures of prion protein expression by immunohistochemical staining. A: No staining (0); B: Weak staining (1+); C: Moderate staining (2+); D: Strong staining (3+).

lymph node involvement. According to the American Joint Committee on Cancer 8th edition staging system, 11 (14.5%), 17 (22.4%), and 48 (63.2%) patients were classified as stages I, II, and III, respectively. Margin-negative (R0) resection was achieved in 63.2% of patients, whereas 35.5% had R1 resection. Most tumors were either well-differentiated (26.3%) or moderately differentiated (65.8%). The mean concentrations of CA19-9 and carcinoembryonic antigen were 957.8 ± 2237.2 U/mL and 8.1 ± 21.0 ng/dL, respectively. Baseline characteristics showed no significant differences between the low and high PrP^{C} groups.

OS and RFS

During the median follow-up period of 31.2 months (ranging from 1 to 137 months), 20 patients (26.3%) were alive without recurrence. The high PrP^{C} group exhibited a shorter median OS of 40.4 months [95% confidence interval (CI): 11.2-59.1] compared to the low PrP^{C} group with a median OS of 137.9 months (95%CI: 72.8-147.1; log-rank test, P = 0.041; Table 2, Figure 2A). Furthermore, the high PrP^{C} group had a shorter median RFS of 13.3 months compared to the low PrP^{C} group with a median RFS of 23.8 months (P = 0.026; Table 2, Figure 2B).

Univariate and multivariate analyses of OS and RFS

Table 3 presents the results of the univariate and multivariate analyses on the prognostic factors influencing OS. The univariate analysis identified tumor size ≥ 5 cm [hazard ratio (HR) = 2.609; 95%CI: 1.218-5.591; P = 0.014], lymph node metastasis (HR = 2.222; 95%CI: 1.039-4.753; P = 0.040), and high PrP^{C} expression (HR = 2.187; 95%CI: 1.015-4.709; P = 0.046) as independent prognostic factors. In the multivariate analysis, tumor size ≥ 5 cm [adjusted HR (aHR) = 2.448; 95%CI: 1.130-5.306; P = 0.023], lymph node metastasis (aHR = 2.633; 95%CI: 1.168-5.936; P = 0.020), and high PrP^{C} expression (aHR = 2.877; 95%CI: 1.260-6.572; P = 0.012) remained independent prognostic factors for OS. Table 4 details the results of univariate and multivariate analyses affecting RFS. The univariate analysis revealed that high PrP^{C} expression (HR = 1.985; 95%CI: 1.071-3.679; P = 0.029) was the only significant prognostic factor.

DISCUSSION

To the best of our knowledge, this is the first study investigating the expression of PrP^{C} in CCA. We found that patients with high intratumoral PrP^{C} expression had significantly shorter OS and RFS compared to those with low intratumoral PrP^{C} expression. Multivariate analysis identified PrP^{C} expression as an independent prognostic factor, similar to established factors such as tumor size and lymph node metastasis. These findings suggest that PrP^{C} expression may serve

Table 1 Patient and tumor characteristics of the study, *n* (%)

Characteristics	Category	Subgroup (based on immunostaining)		Total (*n* = 76)	*P* value
		Low PrP^C (*n* = 38)	High PrP^C (*n* = 38)		
Age (years), mean ± SD		66.7 ± 9.5	66.8 ± 9.8	66.7 ± 9.6	0.953
Male		22 (57.9)	27 (71.1)	49 (64.5)	0.338
BMI (kg/m^2), mean ± SD		24.4 ± 2.9	23.4 ± 2.7	23.9 ± 2.8	0.139
Location	Hilar CCA	22 (57.9)	15 (39.5)	37 (48.7)	0.169
	Intrahepatic CCA	16 (42.1)	23 (60.5)	39 (51.3)	
Tumor size (cm), mean ± SD		4.1 ± 1.9	5.3 ± 3.5	4.7 ± 2.8	0.056
Positive LN		17 (44.7)	17 (44.7)	34 (44.7)	1.000
TNM stage	I	6 (15.8)	5 (13.2)	11 (14.5)	0.890
	II	9 (23.7)	8 (21.1)	17 (22.4)	
	III	23 (60.5)	25 (65.8)	48 (63.2)	
Resection margin	R0	27 (71.1)	21 (55.3)	48 (63.2)	0.262
	R1	11 (28.9)	16 (42.1)	27 (35.5)	
	R2	0 (0.0)	1 (2.6)	1 (1.3)	
Differentiation	WD	8 (21.1)	12 (31.6)	20 (26.3)	0.177
	MD	25 (65.8)	25 (65.8)	50 (65.8)	
	PD	5 (13.2)	1 (2.6)	6 (7.9)	
Laboratory tests	CEA (ng/dL)	5.6 ± 4.4	11.1 ± 31.0	8.1 ± 21.0	0.406
	CA19-9 (U/mL)	813.7 ± 2038.1	1115.9 ± 2461.6	957.8 ± 2237.2	0.591

PrP^C: Cellular prion protein; BMI: Body mass index; LN: Lymph node; TNM: Tumor-node-metastasis; CCA: Cholangiocarcinoma; R0: No cancer cells seen microscopically at the primary tumor site; R1: Cancer cells present microscopically at the primary tumor site; R2: Macroscopic residual tumor at primary cancer site or regional lymph nodes; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; WD: Well-differentiated; MD: Moderately differentiated; PD: Poorly differentiated.

Table 2 Median overall survival and recurrence-free survival according to cellular prion protein expression

Characteristics	Low PrP^C (*n* = 38)	High PrP^C (*n* = 38)	*P* value
Median OS (95%CI), months	137.9 (72.8-147.1)	40.4 (11.2-59.1)	0.041
3-year survival rate (%)	28 (73.7)	27 (71.1)	-
5-year survival rate (%)	27 (71.1)	21 (55.3)	-
Median RFS (95%CI), months	23.8 (15.6-133.6)	13.3 (7.3-31.6)	0.026
3-year recurrence-free rate (%)	20 (52.6)	18 (47.4)	-
5-year recurrence-free rate (%)	19 (50.0)	16 (42.1)	-

PrP^C: Cellular prion protein; OS: Overall survival; CI: Confidence interval; RFS: Recurrence-free survival.

as a postoperative prognostic biomarker of CCA, akin to pancreatic cancer or hepatocellular carcinoma[21,22].

PrP^C is a glycosylphosphatidylinositol-anchored cell surface protein that consists of 208 amino acids[19]. The structure of PrP^C includes a flexible coil in the N-terminal domain and a globular C-terminal domain containing three α-helices and two β-sheets[23]. PrP^C is found not only in the nucleus but also in the mitochondria and Golgi complex[24-26]. Expression of PrP^C begins during embryogenesis and reaches its highest level in adulthood[27,28]. Prion disease is an untreatable, fatal, transmissible neurodegenerative disorder caused by the accumulation of misfolded PrP^{SC} in the brain[29]. Transmissible spongiform encephalopathies caused by PrP^{SC} include sporadic Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, fatal familial insomnia, Gerstmann-Straussler-Scheinker Syndrome, and Kuru[30-32]. PrP^{SC} also plays a substantial role in other neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease by interacting with amyloid-β and α-synuclein[33,34].

Table 3 Univariate and multivariate Cox regression analyses of clinical and radiological parameters affecting overall survival in patients with resected cholangiocarcinoma

Subgroup	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Age ≥ 65 years	0.764 (0.357-1.635)	0.488	-	-
Male	1.496 (0.658-3.400)	0.336	-	-
Tumor size ≥ 5 cm	2.609 (1.218-5.591)	0.014	2.448 (1.130-5.306)	0.023
LN metastasis	2.222 (1.039-4.753)	0.040	2.633 (1.168-5.936)	0.020
Resection margin	2.036 (0.954-4.349)	0.066	-	-
MD tumor (WD as a reference)	1.321 (0.552-3.158)	0.532	-	-
PD tumor (WD as a reference)	1.073 (0.222-5.180)	0.930	-	-
CA19-9 ≥ 37 U/mL	2.248 (0.954-5.296)	0.064	-	-
High PrP^{C}	2.187 (1.015-4.709)	0.046	2.877 (1.260-6.572)	0.012

HR: Hazard ratio; CI: Confidence interval; aHR: Adjusted hazard ratio; LN: Lymph node; MD: Moderately differentiated; WD: Well-differentiated; PD: Poorly differentiated; CA19-9: Carbohydrate antigen 19-9; PrP^{C}: Cellular prion protein.

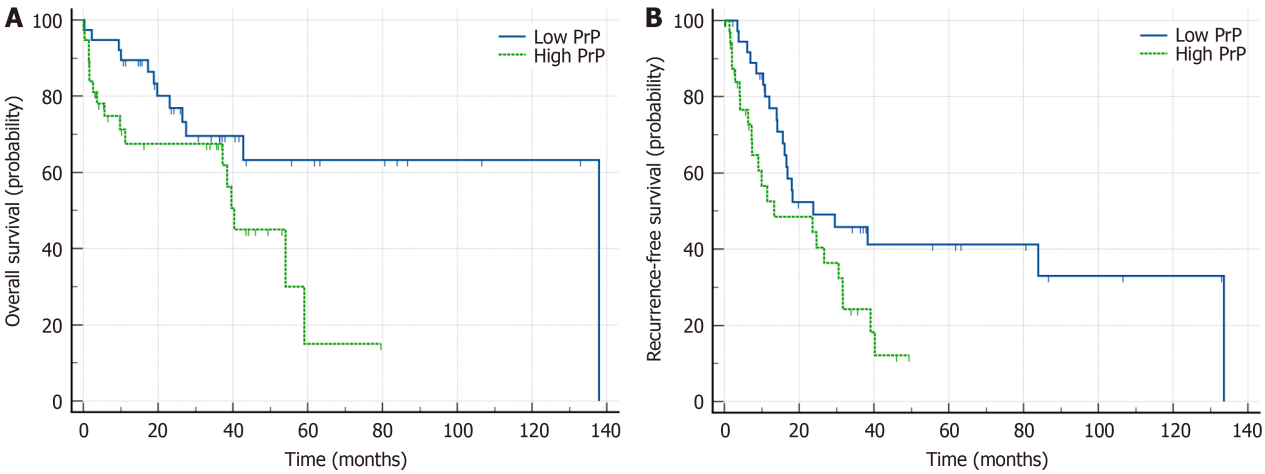

Figure 2 Kaplan Meier survival curves according to prion protein expression. A: Overall survival; B: Recurrence free survival.

PrP^{C} is not only expressed in the central nervous system but also in non-neuronal tissues such as the heart, lungs, lymphocytes, and gastrointestinal tract[28,35,36]. Interestingly, PrP^{C} is involved in several physiological processes, including stress protection, cellular differentiation, mitochondrial homeostasis, circadian rhythm, myelin homeostasis, and immune modulation[27,37]. In addition, PrP^{C} inhibits apoptosis and supports tumor progression by enhancing cancer cell proliferation and metastasis[37-44]. Therefore, PrP^{C} is involved in the development of human cancers including hepatocellular carcinoma[21], pancreatic cancer[45,46], gastric cancer[47], colorectal cancer[48], melanoma[49], and glioblastoma[50] beyond prion disease. PrP^{C} has also been identified in exosomes secreted by cancer cells[51], and such exosomes can promote tumor metastasis by increasing the permeability of endothelial cells and the secretion of angiogenic factors[52]. Recent studies suggest that PrP^{C} contributes to cancer development through various pathways that regulate tumor growth, differentiation, migration, and invasion[53-57]. Cancer tissue exhibits greater genetic instability and increased expression of the *PRNP* gene[44]. Using The Cancer Genome Atlas database, genome-wide association studies analyzing data from 10967 patients with cancer revealed 48 mutations, with eight somatic mutations (G131V, D167N, V180I, D202N, V203I, R208C, R208H, and E211Q) identified as pathogenic[44,58]. Somatic mutations in the *PRNP* gene have been found in various cancers, including lung adenocarcinoma, colorectal adenocarcinoma, endometrial cancer, head and neck squamous cell carcinoma, and melanoma[44]. Overexpression of PrP^{C} is associated with malignant phenotypes of cancer stem cells in various solid tumors[46,59,60]. In contrast, the suppression of PrP^{C} expression impairs proliferation and migration, thereby reducing invasiveness[61-63].

Hypoxia, a common condition in tumor microenvironments due to rapid cell growth outpacing the development of new blood vessels, has a close relationship with PrP^{C}. Under hypoxic conditions, cells often increase survival pathways to adapt to stress, and PrP^{C} has been observed to interact with hypoxia-inducible factor 1-alpha (HIF-1α), a key transcription factor that manages the cellular response to low oxygen levels[64,65]. Since HIF-1α regulates the expression of genes

Table 4 Univariate and multivariate Cox regression analyses of clinical and radiological parameters affecting recurrence-free survival in patients with resected cholangiocarcinoma

Subgroup	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Age ≥ 65 years	0.968 (0.510-1.840)	0.921	-	-
Male	1.163 (0.617-2.193)	0.641	-	-
Tumor size ≥ 5 cm	1.605 (0.816-3.157)	0.170	-	-
LN metastasis	1.484 (0.803-2.746)	0.208	-	-
Resection margin	1.070 (0.563-2.034)	0.837	-	-
MD tumor (WD as a reference)	1.385 (0.686-2.796)	0.363	-	-
PD tumor (WD as a reference)	0.290 (0.037-2.247)	0.236	-	-
CA19-9 ≥ 37 U/mL	1.355 (0.724-2.534)	0.342	-	-
High PrP^{C}	1.985 (1.071-3.679)	0.029	1.985 (1.071-3.679)	0.029

HR: Hazard ratio; CI: Confidence interval; aHR: Adjusted hazard ratio; LN: Lymph node; MD: Moderately differentiated; WD: Well-differentiated; PD: Poorly differentiated; CA19-9: Carbohydrate antigen 19-9; PrP^{C}: Cellular prion protein.

involved in angiogenesis, metabolism, and cell survival, PrP^{C} may indirectly help cancer cells adapt to hypoxic conditions, thus promoting tumor proliferation[66-68]. Growing evidence links increased PrP^{C} expression to the invasiveness of various cancers. HIF-1α plays a pivotal role in cancer progression as its overexpression is implicated in numerous pathways related to angiogenesis, cell proliferation, maintenance of cancer stem cells, promotion of genetic instability, and development of treatment resistance, among others[52,69,70].

High levels of PrP^{C} expression are associated with increased resistance to various types of drugs in glioblastoma, gastric cancer, breast cancer, and colorectal cancer[71-74]. Conversely, the inhibition or knockdown of PrP^{C} induces sensitivity to chemotherapy[35]. In colorectal cancer cells, PrP^{C} is involved in 5-fluorouracil resistance by activating the phosphatidylinositol 3-kinase/protein kinase B signaling pathway and increasing cell survival and proliferation through the expression of cell cycle-related proteins[75]. PrP^{C} can promote multi-drug resistance by upregulating the multidrug resistance p-glycoprotein and inhibiting apoptosis in gastric cancer and breast cancer cells[63,76]. PrP^{C} levels are significantly increased in colorectal cancer cells resistant to 5-fluorouracil and oxaliplatin[75,77]. Increased PrP^{C} expression is also linked with the radiotherapy resistance of tumors. Ionizing radiation can increase the expression of PrP^{C} by activating the ATM-TAK1-PrP^{C} pathway, thereby increasing radiotherapy resistance in glioblastoma, breast cancer, and colon cancer[78]. Taken together, PrP^{C} can regulate several signaling pathways that contribute to cancer resistance. Developing monoclonal antibodies against PrP^{C} and PrP^{C}-specific T cells could be a promising novel approach for creating new compounds for immunotherapy[79].

This study has some potential limitations that should be considered when interpreting the results. First, this is a small-scale study conducted at a single institution, focusing only on intrahepatic and hilar CCA. Therefore, a large-scale study is needed to understand the expression of PrP^{C} in bile duct cancer, including extrahepatic CCA. Second, as this is a retrospective study using existing data, it cannot control for variables that may have been inconsistently or inaccurately recorded, which could lead to selection bias. Third, research on the pathophysiological mechanisms of PrP^{C} in CCA is lacking. Further research is needed to confirm the functional role of PrP^{C} in CCA. Despite these limitations, this study has several strengths. This is the first study, to our knowledge, that explores PrP^{C} expression in patients with surgically removed CCA, offering new insights into the biology of its aggressiveness. Increasing evidence suggests that PrP^{C} is a promising target for cancer treatment, indicating the need for continued research in this field.

CONCLUSION

This study shows that CCA patients with high PrP^{C} expression have shorter postoperative OS and RFS than those with low PrP^{C} expression. The study results suggest that the level of PrP^{C} expression in CCA may serve as a significant prognostic marker following curative surgery.

FOOTNOTES

Author contributions: Shin DW and Cho YA contributed equally to this manuscript as co-first authors. Shin DW and Kim SE contributed to the conceptualization and methodology, and writing-review and editing of this manuscript; Choe JY participated in the data collection; Cho YA took part in the construction of tissue microarray of this study, interpretation of the data and contributed to writing

and revising the manuscript; Park JW and Kim MJ contributed to the data acquisition and analysis; Shin DW and Lee JW contributed to the data analysis and visualization; Shin DW and Moon SH contributed to the software and writing-original draft; Kim SE contributed to the supervision. All authors approved the final version of the manuscript before submission.

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Informed consent statement: Given the study's retrospective design using anonymized clinical data, the requirement for informed consent was waived by the Institutional Review Board of Hallym University Sacred Heart Hospital.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of risk factors for bile leakage after laparoscopic exploration and primary suture of common bile duct

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Abstract

BACKGROUND

Bile leakage is a common complication following laparoscopic common bile duct exploration (LCBDE) with primary duct closure (PDC). Identifying and analyzing the risk factors associated with bile leakage is crucial for improving surgical outcomes.

AIM

To explore the value analysis of common risk factors for bile leakage after LCBDE and PDC, with a focus on strict adherence to indications.

METHODS

Clinical data of 106 cases undergoing LCBDE + PDC in the Hepatobiliary and Pancreatic Surgery Department (Division 1) of Chuzhou First People's Hospital from April 2019 to March 2024 were collected. Retrospective and multiple factor regression analysis were conducted on common risk factors for bile leakage. The change in surgical time was analyzed using the cumulative summation (CUSUM) method, and the minimum number of cases required to complete the learning curve for PDC was obtained based on the proposed fitting curve by identifying the CUSUM maximum value.

RESULTS

Multifactor logistic regression analysis showed that fibrinous inflammation and direct bilirubin/indirect bilirubin were significant independent high-risk factors for postoperative bile leakage ($P < 0.05$). The time to drain removal and length of

hospital stay in cases without bile leakage were significantly shorter than in cases with bile leakage ($P < 0.05$), with statistical significance. The CUSUM method indicated that a minimum of 51 cases were required for the surgeon to complete the learning curve ($P = 0.023$).

CONCLUSION
With a good assessment of duodenal papilla sphincter function, unobstructed bile-pancreatic duct convergence, exact stone clearance, and sufficient surgical experience to complete the learning curve, PDC remains the preferred method for bile duct closure and is worthy of clinical promotion.

Key Words: Laparoscopic common bile duct exploration; Primary duct closure; Bile leakage; Risk factor analysis; Cumulative summation

Core Tip: This study identifies key risk factors for bile leakage following laparoscopic common bile duct exploration and primary duct closure (PDC). Through retrospective analysis and logistic regression, fibrinous exudation and direct bilirubin/indirect bilirubin were found to be significant independent risk factors. The cumulative summation method demonstrated that a minimum of 51 cases is required for surgeons to master the PDC technique effectively. Proper assessment of duodenal papilla function, ensuring bile duct patency, and achieving surgical proficiency are essential for minimizing complications. Adhering to these guidelines may optimize patient outcomes and promote PDC as a preferred method in clinical practice.

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INTRODUCTION

Laparoscopic common bile duct exploration (LCBDE) as a mature surgical method for treating intrahepatic and extrahepatic bile duct stones has undergone more than a century of development[1-4]. With the continuous advancement of medical technology, especially the use of high-definition laparoscopy, high-definition cholangioscopy, and stone fragmentation techniques, the minimally invasive and effectiveness of LCBDE have been significantly improved. In recent years, an increasing number of studies support the use of primary duct closure (PDC) rather than the traditional T-tube drainage (TTD) as the preferred method for bile duct repair after LCBDE, early literature indicates that although the first common bile duct exploration performed in 1889 used PDC for bile duct repair, TTD remains the primary method for duct repair after common bile duct exploration today, and PDC has not gained the widespread application initially expected[5-7]. With advancements in high-definition laparoscopy, high-definition cholangioscopy, and stone fragmentation techniques, the minimally invasive nature and effectiveness of LCBDE have significantly improved. Research shows that PDC is superior to TTD in terms of safety and minimally invasive nature, with no significant difference in efficacy. However, the indications and contraindications for PDC are not clearly defined. Despite PDC becoming a routine procedure in large hepatobiliary surgical centers, its global adoption rate remains low, mainly due to concerns among doctors and patients about potential complications after PDC[8,9]. However, despite PDC becoming a routine procedure in large hepatobiliary surgical centers, its adoption rate in broader medical practice remains low. This is mainly due to concerns among doctors and patients about potential complications such as bile leakage and bile duct strictures after PDC.

This study aims to explore how, under strict control of surgical indications, analyzing known risk factors for bile leakage after PDC can further optimize surgical strategies and reduce the incidence of complications. The research will summarize and analyze factors that may lead to bile leakage after PDC, including but not limited to patient age, bile duct diameter, severity of cholangitis, bile duct injury during surgery, and postoperative bile duct pressure. The role of multidisciplinary team collaboration, including surgeons, anesthesiologists, nursing teams, and radiologists, is increasingly recognized in improving the success rate of PDC. The exact risk factors for bile leakage after PDC are not yet fully understood. This study aims to explore how, under strict control of surgical indications, analyzing known risk factors for bile leakage after PDC can further optimize surgical strategies and reduce the incidence of complications. The research will also explore how collaboration among multidisciplinary teams, including surgeons, anesthesiologists, nursing teams, and radiologists, can improve the success rate of PDC. Furthermore, the study will evaluate the role of preoperative imaging studies in predicting the risk of bile leakage and the importance of intraoperative cholangiography in determining bile duct repair strategies.

MATERIALS AND METHODS

Study population

A total of 106 cases were included in this study, consisting of patients who underwent LCBDE + PDC for liver extrahepatic bile duct stones (or combined with gallstones) from January 2019 to April 2024 at the First People's Hospital of Chuzhou City. Among them, there were 46 males (43.4%) and 60 females (56.6%). The comorbidities included: History of diabetes in 6 cases (5.66%), history of hypertension in 36 cases (33.96%), history of previous laparoscopic common surgery in 11 cases (10.38%), and history of acute pancreatitis in 3 cases (2.83%). Postoperatively, bile leakage occurred in 12 cases (11.32%), all of which were classified as grade 1 complications according to the Clavien-Dindo classification, and were managed with conservative observation leading to self-healing and discharge upon recovery. This study was approved by our hospital's ethics committee. Patients and their families signed informed consent forms before the surgery.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with common bile duct dilation or suspected common bile duct lesions with negative exploration results; (2) Patients who have had their common bile duct stones removed completely and the end of the common bile duct is unobstructed; (3) Patients with gallbladder stones, common bile duct stones, and distal obstruction or stenosis of the common bile duct all effectively treated during surgery; (4) After completing the first stage suture surgery, observe the absence of sustained obvious bile leakage at the incision site of the common bile duct; and (5) Those who have successfully retained nasobiliary drainage before or during surgery.

Exclusion criteria: (1) Residual stones in the extrahepatic bile duct and stenosis at the end of the common bile duct that were not treated or treated satisfactorily during surgery; (2) Intrahepatic bile duct stones combined with intrahepatic bile duct stenosis; (3) Long term, reliable, and unobstructed external drainage of the bile duct is required due to the primary disease; (4) Elderly patients with biliary and pancreatic duct diseases; and (5) Combine patients with severe cardiovascular and pulmonary diseases.

Surgical methods

Complete cholecystectomy according to standard laparoscopic common operating procedures; Fully expose the common bile duct (free descending duodenal bulb if necessary), use low-power electrocoagulation (30 W) to occlude the serosal vascular network of the anterior wall of the bile duct, and make a sharp longitudinal incision of about 0.6 cm of the anterior wall of the common bile duct (depending on the size of the stone); Complete cholangioscopy for stone removal, clear infectious fibrous exudate, fully evaluate the function and patency of the duodenal papilla, and ensure accurate stone removal; Adopt intermittent/continuous suture of bile duct incision (suture selection: 4-0 Vicryl suture); Take out the specimen, rinse the surgical area, observe and rule out bile leakage, and then place a drainage tube at the lesser omentum hole to fix it by pulling out a trocar 5 mm below the right rib margin. Under direct visualization, remove each trocar and suture the incision layer by layer. Postoperative management includes monitoring the abdominal drainage tube: Closely observe the volume and nature of bile drainage. If bile is continuously drained for 3 days postoperatively or the single-day drainage volume is ≥ 100 mL, bile leakage may be indicated. For patients without a drainage tube, monitor for signs of peritoneal irritation. If necessary, perform abdominal puncture to check for bile. Suspected bile leakage can be confirmed *via* intraoperative cholangiography. Prompt control of infections secondary to bile leakage is crucial to avoid contraindications for surgical treatment. Provide appropriate nutritional support to aid recovery. Criteria for determining bile leakage typically include: Continuous bile drainage from the abdominal tube for 3 days post-surgery or single-day drainage volume ≥ 100 mL. For those without a drainage tube, signs of peritoneal irritation, bile extracted *via* abdominal puncture, or intra-abdominal bile found during reoperation. Detection of contrast agent accumulation outside the biliary system through intraoperative cholangiography or postoperative imaging (*e.g.*, computed tomography, magnetic resonance imaging) suggests bile leakage. Symptoms like fever, abdominal pain, and tenderness, along with laboratory findings (*e.g.*, elevated white blood cell count), support the diagnosis of bile leakage.

Observation indicators and follow-up

Monitor postoperative drainage volume (mL/day) to determine the presence of bile leakage, surgical time, postoperative extubation time, postoperative discharge time, and total hospitalization costs. All cases were followed up routinely for 6-12 months after surgery, and no fluid accumulation, bile duct stenosis, stone recurrence.

Learning curve

Apply the cumulative summation (CUSUM) method to analyze the changes in surgical time. Representing the actual surgical time of each patient and the average surgical time of the same group of patients. Calculate the deviation between the actual surgical time value and the average surgical time value for each patient, and obtain CUSUM by summing multiple times. The calculation formula for this study is as follows: Sort the samples in the order of surgery and edit the serial numbers. Draw a scatter plot with CUSUM value as the vertical axis and number of cases as the horizontal axis, and then perform curve fitting. The fitting coefficient was used to determine the degree of fitting, and linear, quadratic, and cubic fitting were performed separately. The closer the value is to 1, the better the fitted curve.

Statistical analysis

This article uses SPSS 27.0 and R 4.3.2 to process and analyze the data. Continuous data is represented in the form of mean ± SD, while categorical data is represented in the form of frequency (percentage). Single factor logistic regression

was used to analyze the risk factors for bile leakage, and multiple factor logistic regression was used to analyze the independent risk factors for bile leakage. The differences were statistically significant with $P < 0.05$ in the entire study. The rank sum test is used to analyze whether postoperative bile leakage has a significant impact on extubation time, discharge time, and total hospitalization costs. Construct a learning curve using CUSUM and fit it.

RESULTS

Using single factor logistic regression to screen risk factors

A single factor logistic regression model was established with total bilirubin, straight to straight ratio, history of diabetes, operation time, number of cases of surgery, history of hypertension, suture mode, incidence, common bile duct stones (single, multiple, discharged stones, fibrinous exudation, microstones), gallstones (microstones, multiple), grass to propylene ratio, albumin, white blood cell, total bile acid, hemoglobin, γ-glutamyl transpeptidase, C-reactive protein, common bile duct diameter, carbohydrate antigen 199, alkaline phosphatase, and other factors as independent variables, and whether bile leakage occurred after surgery as dependent variables (Tables 1 and 2). From the above results, it can be concluded that common bile duct stones (fibrinous exudation), total bilirubin, and direct bilirubin/indirect bilirubin ratio (direct to indirect ratio) have a significant impact on whether bile leakage occurs after surgery ($P < 0.05$), and are risk factors for postoperative bile leakage.

Using multiple logistic regression to screen independent risk factors

Perform multiple logistic regression analysis using factors that have a significant impact on single factor logistic regression as independent variables, as shown in Table 3. The above results indicate that common bile duct stones (cellulose) and the ratio of direct bilirubin/indirect bilirubin are independent risk factors for postoperative bile leakage ($P < 0.05$).

The impact of bile leakage on extubation time, discharge time, and total hospitalization costs

The rank sum test was used to examine whether bile leakage had a significant impact on extubation time, discharge time, and total hospitalization costs. The results are as follows (Table 4). The above results show that patients who did not experience bile leakage after surgery had significantly shorter extubation time and discharge time compared to patients who experienced bile leakage after surgery, with $P < 0.05$ and statistical significance.

Learning curve

Obtain three fitting curves: Based on the proposed fitting curve, find the case number 51 with the maximum CUSUM value, which is the minimum number of surgeries required to cross the learning curve. The curve can be divided into two stages of surgical maturity, namely the stage of technical improvement and the stage of proficiency, based on the maximum value of CUSUM, which is 51. Using two groups as independent variables and postoperative bile leakage as the dependent variable, the logistic regression model shows that the surgical maturity stage significantly affects the occurrence of postoperative bile leakage ($P = 0.023$, Figure 1). The schematic diagram of gallbladder inflammation is shown in Figure 2 below.

DISCUSSION

The comprehensive evaluation of the duodenal papilla function of the duodenal papilla includes the sphincter of Oddi (SO) [mainly involving the contraction and relaxation function of the bile duct sphincter and the ampulla sphincter, as well as the smooth flow of the bile and pancreatic ducts, and diseases leading to So dysfunction (SOD)] mainly include: Fibrosis or chronic inflammation-induced Oddi sphincter stenosis: This is one cause of SOD, where fibrosis or chronic inflammation of the sphincter leads to narrowing, affecting the normal flow of bile and pancreatic juices. Congenital sphincter hypertrophy, and neuromuscular or hormonal factors causing intermittent spasmodic dysfunction: These causes involve congenital issues or abnormal neurohormonal regulation, leading to functional abnormalities of the Oddi sphincter. Post-cholecystectomy dysfunction: After gallbladder removal, the Oddi sphincter may experience dysfunction due to the loss of the gallbladder's regulatory effect on bile duct pressure, leading to bile excretion disorders and SOD. Oddi sphincter dysfunction refers to a series of clinical syndromes caused by structural or functional abnormalities of the bile duct and/or pancreatic duct sphincter[10-12]. Low pressure in the bile duct and smooth flow in the bile and pancreatic duct junction are necessary prerequisites for effective healing of the bile duct first-phase incision and reducing bile leakage. For different levels of patency at the distal end of the laparoscopic common bile duct[13], laparoscopic duodenal papilla step by step dilatable catheter dilatation or laparoscopic duodenal papilla balloon dilatation is adopted. When necessary, laparoscopic endoscopic nasobiliary drainage or laparoscopic common bile duct stent is performed to ensure the patency of the duodenal papilla and maintain low pressure in the bile duct.

In this study, cases that did not undergo first-phase incision were mostly those in whom effective stone clearance could not be guaranteed, the conditions for bile duct wall closure were inadequate (such as significant needle hole leakage requiring multiple needle-point sutures but still unsatisfactory), severe bile duct inflammation requiring extended biliary decompression to increase perioperative safety and smooth recovery, a patient population unable to tolerate secondary surgery due to complications such as bile leakage, and the presence of factors such as liver hilum tumor that may lead to

Table 1 Data summary and analysis, *n* (%)

Characteristic		Overall	No bile leakage occurs	Gallbladder leakage occurs
Gallstones-multiple	No	90 (84.91)	78 (100)	12 (100)
	Yes	16 (15.09)	16 (0)	0 (0)
Gallstones-micro stones	No	78 (73.58)	69 (75)	9 (75)
	Yes	28 (26.42)	25 (25)	3 (25)
Gallstones-post laparoscopic common surgery	No	93 (87.74)	86 (58.33)	7 (58.33)
	Yes	13 (12.26)	8 (41.67)	5 (41.67)
Common bile duct stones-single	No	67 (63.21)	60 (58.33)	7 (58.33)
	Yes	39 (36.79)	34 (41.67)	5 (41.67)
Common bile duct stones	No	52 (49.06)	47 (41.67)	5 (41.67)
	Yes	54 (50.94)	47 (58.33)	7 (58.33)
Common bile duct stones-micro stones	No	37 (34.91)	34 (36.17)	3 (25)
	Yes	69 (65.09)	60 (63.83)	9 (75)
Common bile duct stones-cellulose	No	72 (67.92)	69 (73.40)	3 (25)
	Yes	34 (32.08)	25 (26.60)	9 (75)
Common bile duct stones	No	103 (97.17)	91 (100)	12 (100)
	Yes	3 (2.83)	3 (0)	0 (0)
CBD	5-6	7 (6.6)	6 (8.33)	1 (8.33)
	6-7	17 (16.04)	15 (16.67)	2 (16.67)
	7-8	16 (15.09)	15 (8.33)	1 (8.33)
	8-9	18 (16.98)	15 (25)	3 (25)
	> 9	48 (45.28)	43 (41.67)	5 (41.67)
Factors, mean ± SD				
WBC		7.35 ± 3.36	7.57 ± 3.39	5.64 ± 2.56
HB		132.1 ± 16.42	132.23 ± 17.15	131.08 ± 9.23
CRP		22.42 ± 46.68	23.91 ± 48.38	10.76 ± 29.06
CA199		99.06 ± 361.33	72.21 ± 283.09	233.27 ± 628.95
Total bilirubin		41.33 ± 36.58	43.91 ± 37.93	21.13 ± 10.4
Directly increase the proportion		2.64 ± 3.06	19.48 ± 21.73	7.04 ± 6.6
Indirect increase ratio		1.52 ± 1.13	24.43 ± 17.75	14.09 ± 4.93
Straight to straight ratio		0.82 ± 0.45	0.87 ± 0.44	0.45 ± 0.28
Albumin		43.48 ± 5.09	1.6 ± 1.18	0.93 ± 0.32
ALT/AST		0.76 ± 0.52	0.94 ± 0.98	0.36 ± 0.07
GGT		308.09 ± 289.23	43.52 ± 5.19	43.16 ± 4.39
ALP		166.2 ± 133.37	223.04 ± 241.17	73.29 ± 90.76
TBA		33.2 ± 54.3	130.9 ± 161.17	41.76 ± 39.36
Operative time		89.42 ± 28.76	0.75 ± 0.53	0.77 ± 0.4

CBD: Common bile duct diameter; WBC: White blood cell; HB: Hemoglobin; CRP: C-reactive protein; CA199: Carbohydrate antigen 199; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transpeptidase; ALP: Alkaline phosphatase; TBA: Total bile acid.

Table 2 Single factor logistic regression screening for risk factors

Factors	Coefficient	*Z* value	*P* value
Incidence	-0.9614	-1.5464	0.1220
History of diabetes	1.5041	1.6209	0.1050
History of hypertension	1.1436	1.8248	0.0680
Gallstones-multiple	-16.6943	-0.0102	0.9918
Gallstones-micro stones	-0.0834	-0.1180	0.9060
Common bile duct stones-single	0.2315	0.3712	0.7105
Common bile duct stones	0.3365	0.5420	0.5878
Common bile duct stones-micro stones	0.5306	0.7576	0.4487
Common bile duct stones-cellulose	2.1138	2.9930	0.0028
Common bile duct stones	-14.5401	-0.0105	0.9916
CBD	-0.2231	-0.1695	0.8654
WBC	-0.2557	-1.8175	0.0691
HB	-0.0043	-0.2297	0.8183
CRP	-0.0105	-0.8830	0.3772
CA199	0.0009	1.1705	0.2418
Total bilirubin	-0.0506	-2.0312	0.0422
Direct/indirect bilirubin	-7.0321	-2.8225	0.0048
Albumin	0.0000	0.0000	1.0000
ALT/AST	0.0731	0.1259	0.8998
GGT	0.0000	0.0000	1.0000
ALP	-0.0065	-1.3364	0.1814
TBA	-0.0024	-0.3707	0.7109
Operative time	0.0157	1.7035	0.0885
Suture method	0.3221	0.4915	0.6231

CBD: Common bile duct diameter; WBC: White blood cell; HB: Hemoglobin; CRP: C-reactive protein; CA199: Carbohydrate antigen 199; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transpeptidase; ALP: Alkaline phosphatase; TBA: Total bile acid.

Table 3 Multivariate logistic regression analysis

Factor	Partial regression coefficient	Error	*Z* value	*P* value	OR	95%CI
Common bile duct stones-cellulose	1.97008	0.77372	2.546	0.0109	7.171	1.705-38.400
Total bilirubin	-0.03732	0.02841	-1.314	0.189	0.963	0.903-1.010
Direct/indirect bilirubin	-5.60348	2.43206	-2.304	0.0212	0.004	0.000-0.154

OR: Odds ratio; CI: Confidence interval.

short-term extrinsic bile duct obstruction preventing the intraoperative placement of initial stents, advising against first-phase incision to prevent serious complications such as bile leakage and secondary surgeries, especially in elderly patients with relative contraindications.

Assessing the diameter of the common bile duct during surgery may be limited by factors such as differences in surgeons, inflammation of surrounding bile duct tissues preventing full visualization, and lack of effective measuring tools. Clinically, preoperative evaluations of the inner diameter of the common bile duct through methods such as color Doppler ultrasound, computed tomography, magnetic resonance cholangiopancreatography are more objective. However, the timing and methods of measurements using these various techniques differ, leading to significant variations in clinical measurements. In this study, millimeter intervals were used as the width of the common bile duct (the

Table 4 The impact of bile leakage on extubation time, discharge time, and total hospitalization costs, mean ± SD

Factors	No bile leakage occurs	Gallbladder leakage occurs	*Z* value	*P* value
Pull out time	3.61 ± 1.25	5.33 ± 2.81	-2.627	0.009
Discharge time	5.77 ± 1.44	8.67 ± 6.49	-2.105	0.035
Total hospitalization expenses	15913.7 ± 3246.7	17249.28 ± 4344.86	-0.648	0.517

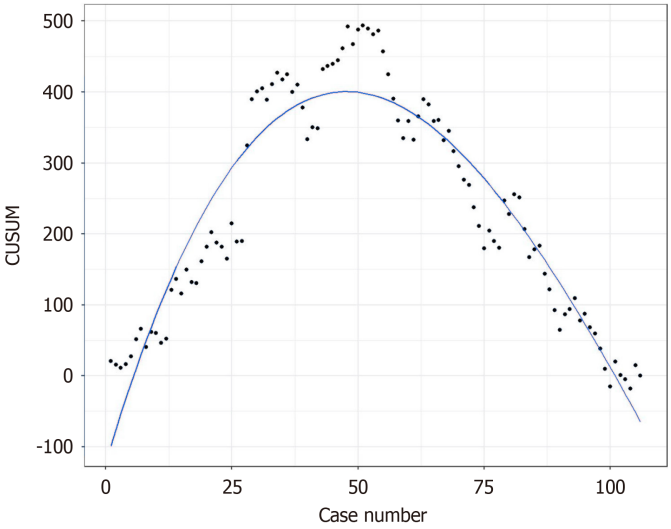

Figure 1 Learning curve. The samples were sorted according to the order of surgery and the serial number was edited. The % scatter plot was drawn with cumulative summation value as the vertical axis and the number of cases as the horizontal axis. CUSUM: Cumulative summation, $\mathrm{CUSUM} = \sum_{i=1}^{n} (x_i - u)$.

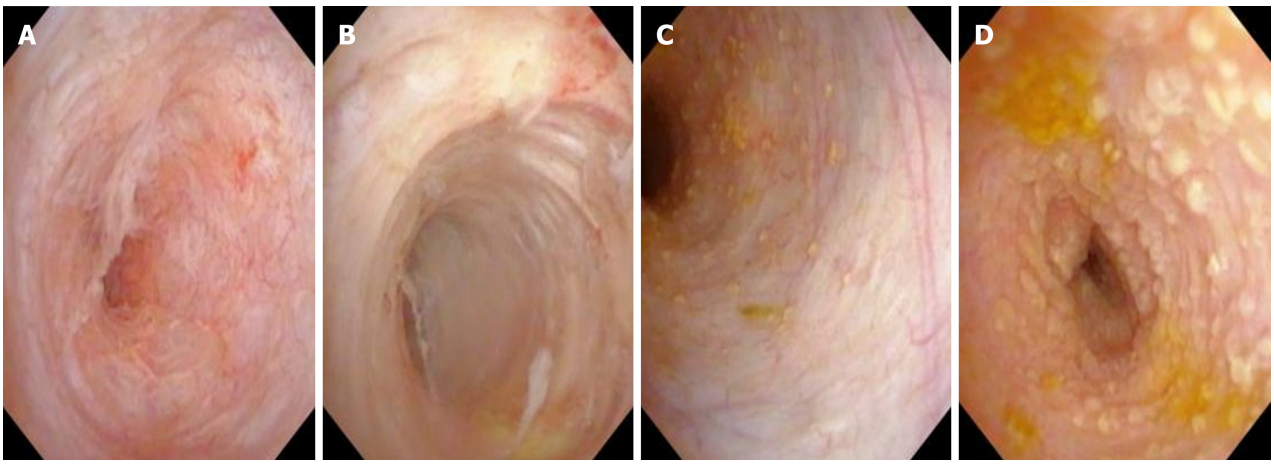

Figure 2 Gallbladder inflammation. A: The fibrous membrane covering the bile duct has not yet affected the patency of the nipple; B: The fibrous membrane in the bile duct affects the patency of the nipple; C: Nodular hyperplasia of bile duct mucosa (local); D: Nodular hyperplasia of bile duct mucosa (involving the entire bile duct mucosa).

shortest length among the three examinations) for single-factor regression analysis regarding the occurrence of bile leakage, showing no significant statistical significance ($P > 0.05$).

For patients with common bile duct dilation greater than 8 cm, numerous clinical studies have confirmed that first-phase incision is safe and effective[14-16]. Given the lack of muscle layer in the extrahepatic bile ducts (primarily referring to the common bile duct), for patients with significant dilation (distinct from bile duct dilation), bile stasis, stone recurrence, and other long-term complications merit further clinical research. Animal experiments have shown that longitudinal incision of the bile duct does not lead to scar healing[17]. For individuals with a normal bile duct diameter that does not dilate due to sustained increase in bile duct pressure, it can be assumed that the SO function can maintain a good state of low pressure in the bile duct. This provides a theoretical basis for populations with smaller bile duct diameters. This study suggests that for patients with a common bile duct diameter < 8 mm, PDC can be safely performed without increasing the risk of long-term complications related to bile duct stricture.

Fibrinous inflammation often occurs on the mucous and serous membranes, referring to inflammatory exudate containing a large amount of fibrin protein. When there is biliary tract infection, the exuded fibrin, neutrophils, and necrotic mucosal tissues (the exuded fibrin coagulates) form a thin yellowish, elastic membrane covering the bile duct mucosa, known as pseudomembranous inflammation, which is often easily peeled off[18-21]. The substantial exudation of fibrinogen indicates severe vascular wall damage. In this study, the analysis of fibrinous exudate in the bile characteristic of acute biliary infection as a variable using single-factor and multi-factor regression analysis revealed that it is an independent risk factor for bile leakage postoperatively. In clinical practice, using basket retrieval for rotational removal, flushing of the bile duct is essential to ensure complete removal of intraluminal fibrinous covering, promoting smooth bile drainage and reducing the pressure buildup from bile stasis. Although the presence of fibrinous exudate in the common bile duct is an independent risk factor, the postoperative complication score for bile leakage (Clavien-Dindo classification) is grade 1, resolving with conservative observation. However, special attention is warranted for elderly patients, those with poor duodenal papillary function and patency, emphasizing cautious use of PDC.

Common suture techniques in clinical practice mainly include interrupted and continuous sutures; interrupted sutures are slower, have multiple knots, and are less effective in knotting outside the lumen, leading to slightly inferior hemostatic effects. The advantages of continuous sutures are less time-consuming, all knots are positioned outside the lumen, providing good hemostasis, yet disadvantages include a higher risk of tearing the thin and fragile bile duct wall, difficulty stitching into the biliary duct embedded in liver tissue, loose tying may result in bile leakage, while tight tension can lead to stricture at the anastomosis of tiny bile ducts.

Bile leakage post-PDC is often attributed to factors such as loose suture threads, minor leaks at the incision ends, or suture thread rupture at needle holes in thin-walled and narrow-bore bile ducts; increasingly, studies are optimizing the suture techniques for biliary ducts post-PDC, such as barbed suture (knotless) continuous sutures, layered sutures, full-thickness continuous eversion sutures, dual-needle bidirectional continuous sutures, and fibrin sealant coating[22-26]. Each suture technique has its advantages and disadvantages, balancing safety and trauma considerations, effectively reducing bile leak volume, and ease of adoption. These novel suture techniques have shown excellent clinical outcomes, worthy of further in-depth research in clinical practice.

Combining previous explorations, the author's team has recently utilized the "continuous double-layer *U*-stitching technique," achieving good clinical results. This technique can effectively prevent repeated pulling on the "first knot" and the suture segments (avoiding suture damage), reduce bile duct wall cutting (needle hole leaks), maintain consistent tension throughout (avoiding loose suture segments), promote tight and organized suture segments through a terminal "tissue knot," effectively utilize peritoneal layer coverage to protect the biliary duct suture area, and reduce the impact of increased bile duct pressure on incision tension.

Jaundice resulting from elevated bilirubin levels can be roughly categorized as hepatocellular or obstructive; jaundice caused by biliary tract stones is primarily due to direct bilirubin elevation. Single-factor logistic regression analysis in this study indicates that the total bilirubin range for individuals without bile leakage is 43.91 ± 37.93 μmol/L, while the range for those with bile leakage is 21.13 ± 10.4 μmol/L, with a P value of 0.0422; the direct bilirubin ratio range for individuals without bile leakage is 0.87 ± 0.44, while that for individuals with bile leakage is 0.45 ± 0.28, with a P value of 0.0048, both being risk factors for postoperative bile leakage. Multi-factor logistic regression analysis demonstrates that the direct bilirubin ratio is an independent risk factor for bile leakage occurrence. This ratio is often overlooked in clinical practice, especially when the total bilirubin level is normal or mildly elevated, increasing the risk of bile leakage, emphasizing the need for further research and attention in clinical practice.

CONCLUSION

In the evaluation of duodenal papillary sphincter function, patency of the common bile duct and pancreatic duct, and successful completion of the learning curve for stone clearance, PDC remains the preferred method for biliary duct closure. The surgical strategy for common bile duct stones in the era of endoscopy needs further exploration and research in order to optimize management, improve patient outcomes, and minimize risks.

FOOTNOTES

Author contributions: Yang QS contributed to the study design and data analysis; Zhang M, Ma CS, Teng D, Li A, Dong JD, and Wang XF assisted with data collection and interpretation; Liu FB provided critical revisions and clinical insights, supervised the research and served as the corresponding author; and all authors thoroughly reviewed and endorsed the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Clinical outcomes of interlocking main pancreatic duct-jejunal internal bridge drainage in middle pancreatectomy: A comparative study

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Abstract

BACKGROUND

Middle pancreatectomy (MP) is a surgical procedure that removes non-invasive lesions in the pancreatic neck and body, allowing for the preservation of pancreatic function. However, MP is associated with a higher risk of postoperative complications, and there's no clear consensus on which anastomotic method is preferable. In recent years, our team has developed a new method called interlocking main pancreatic duct-jejunal (IMPD-J) internal bridge drainage to MP.

AIM

To compare perioperative and postoperative outcomes in patients who underwent IMPD-J bridge drainage and those underwent traditional duct-to-mucosa pancreatojejunostomy.

METHODS

Patients who underwent MP in our hospital between October 1, 2011 and July 31, 2023 were enrolled in this study. Patients were divided into two groups based on their pancreatojejunostomy technique: IMPD-J bridge drainage group and duct-to-mucosa pancreatojejunostomy group. Demographic data (age, gender, body mass index, hypertension, diabetes, *etc.*) and perioperative indicators [operation time, intraoperative bleeding, clinically relevant postoperative pancreatic fistula (CR-POPF), delayed gastric emptying, *etc.*] were recorded and analyzed statistically.

RESULTS

A total of 53 patients were enrolled in this study, including 23 in the IMPD-J Bridge Drainage group and 30 in the traditional duct-to-mucosa pancreatojejunostomy group. There were no significant differences in demographic or preoperative characteristics between the groups. Compared to traditional duct-to-

mucosa pancreaticojejunostomy, IMPD-J bridge drainage had a significant shorter operation time (4.3 ± 1.3 hours *vs* 5.8 ± 1.8 hours, P = 0.002), nasogastric tube retention days (5.3 ± 1.7 days *vs* 6.5 ± 2.0 days, P = 0.031), lower incidence of delayed gastric emptying (8.7% *vs* 36.7%, P = 0.019), and lower incidence of CR-POPF (39.1% *vs* 70.0%, P = 0.025). Multivariate logistic regression analysis showed that pancreaticojejunostomy type (odds ratio = 4.219, 95% confidence interval = 1.238-14.379, P = 0.021) and plasma prealbumin (odds ratio = 1.132, 95% confidence interval = 1.001-1.281, P = 0.049) were independent risk factor for CR-POPF. In IMPD-J bridge drainage group, only one patient experienced recurrent pancreatitis due to the large diameter of the silicone tube and had it removed six months after surgery.

CONCLUSION

Compared to traditional duct-to-mucosa pancreatojejunostomy, IMPD-J bridge drainage has the advantages of simplicity and fewer perioperative complications, with favorable long-term outcomes.

Key Words: Middle pancreatectomy; Pancreaticojejunostomy; Duct-to-mucosa pancreaticojejunostomy; Clinically relevant postoperative pancreatic fistula; Delayed gastric emptying; Perioperative and postoperative complications

Core Tip: Interlocking main pancreatic duct-jejunal bridge drainage emerges as a promising technique for middle pancreatectomy, offering shorter operation time, reduced risk of clinically relevant postoperative pancreatic fistula and delayed gastric emptying, and favorable long-term safety. Compared to traditional duct-to-mucosa pancreatojejunostomy, interlocking main pancreatic duct-jejunal bridge drainage demonstrates simplicity and fewer perioperative complications, suggesting its potential as a preferred method in middle pancreatectomy procedures.

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INTRODUCTION

Middle Pancreatectomy (MP) is a surgical technique primarily used to treat non-invasive lesions in the neck and body of the pancreas. As a parenchyma-sparing operation, it was first applied in 1957 by Guillemin and Bessot[1] on a patient with chronic pancreatitis. This method is designed to preserve as much normal pancreatic tissue as possible, thereby reducing the risk of both exocrine and endocrine insufficiency post-surgery. The technique is particularly advantageous for younger patients[2], where the preservation of pancreatic function can have a more significant impact on long-term outcomes. Despite its benefits, MP has not been widely adopted in clinical practice. The main reason is that compared with conventional pancreatic surgeries such as pancreaticoduodenectomy and pancreatic distal resection, MP is associated with a higher risk of postoperative complications, including postoperative pancreatic fistula (POPF), post-pancreatectomy hemorrhage, and delayed gastric emptying (DGE). POPF, in particular, has a high occurrence rate, with studies indicating that its incidence can reach up to 80.8%[3]. This increased risk is often attributed to the creation of two pancreatic stumps during MP surgery, thereby increasing the risk of pancreatic anastomotic leakage. In response to this risk, clinicians have explored various techniques to manage the stumps, such as duct-to-mucosa pancreaticojejunostomy, double pancreaticojejunostomy[4], pancreatogastrostomy, and the use of biomaterial coverage. Although duct-to-mucosa pancreaticojejunostomy is commonly used[5], no single technique has been proven to be optimal. In addition, the complex and time-consuming nature of the MP procedure further contributes to its lower utilization in clinical settings. According to a meta-analysis study published in 2022[6], traditional anastomosis requires additional Roux-en-Y gastrointestinal reconstruction after resection of the pancreatic mass, which increases the difficulty of the operation. When using laparoscopic or robot-assisted surgery, this complexity is particularly evident due to the restricted operating space and the need for hand-eye coordination in a confined environment, which amplifies the challenges. These factors collectively limit the broader adoption of MP, emphasizing the need for continued research and the development of more effective and streamlined techniques to reduce the risks and complications associated with this surgical approach.

Interlocking main pancreatic duct-jejunal (IMPD-J) internal bridge drainage is a novel pancreaticojejunostomy technique pioneered by our hospital. This surgical method was initially performed on a patient with anastomotic dehiscence of pancreaticojejunostomy in 2006[7]. The patient developed a pancreaticojejunostomy fistula on the 6th day after surgery, accompanied by fever, abdominal pain, elevated amylase in the drainage fluid, and obvious peritoneal irritation symptoms. Abdominal ultrasonography revealed a large amount of fluid in the upper abdomen. After exploratory laparotomy, there was a severe anastomotic dehiscence, and the length of the dehiscence exceeding half the circumference of the anastomosis. In this situation, simple reoperation or local drainage was not feasible. Therefore, we inserted one end of a silicone drainage tube into the main pancreatic duct and fixed the other end with embedded sutures

in the lumen of the jejunal loop, with the aim of draining pancreatic secretions into the distal jejunum. The postoperative recovery was successful, and the patient was discharged 34 days after surgery, without any signs of diabetes or pseudocyst formation during follow-up. This surgical method was later applied to two other patients with severe pancreaticojejunostomy fistulas, with similar favorable outcomes. Due to its lower incidence of POPF rate, simplicity of operation, and suitability for minimally invasive surgery in limited visual fields, this IMPD-J bridge drainage surgical method is widely adopted by our team. After years of application, this retrospective study aimed to explore whether IMPD-J bridge drainage was superior to traditional pancreatic duct-to-mucosa anastomosis, as well as to evaluate its long-term safety. The results of this study could guide surgeons in adopting more effective and safer methods for pancreaticojejunostomy, ultimately improving patient outcomes and reducing complications.

MATERIALS AND METHODS

Patients

Demographic and surgical data of patients who underwent MP surgery in the First General Surgery Department of Shengjing Hospital Affiliated to China Medical University between October 1, 2011, and July 31, 2023, were collected for this study. The inclusion criteria included: (1) Patients who had MP surgery; and (2) Patients whose distal pancreatic procedures involved pancreaticojejunostomy. The exclusion criteria were: (1) Patients who had emergency surgery; (2) Patients with other significant illnesses; and (3) Patients with a history of abdominal surgery. This study was approval by the Ethics Committee of Shengjing Hospital (approval No. 2024PS903K).

Data collection and outcome assessment

Preoperative, intraoperative and postoperative data were collected to compare the effectiveness and safety outcomes. Preoperative data included gender, age, body mass index (BMI), history of hypertension, history of diabetes, smoking history, alcohol consumption history, and preoperative laboratory indicators [white blood cells (WBCs), neutrophils, red blood cells, platelets, total protein, albumin, prealbumin, and total bilirubin]. Intraoperative data included the maximum tumor diameter, the diameter of the main pancreatic duct, total operation time, intraoperative blood loss, and transfusion volume. Postoperative outcomes include the incidence of clinically relevant POPF (CR-POPF), duration of nasogastric tube retention, the incidence of DGE, incidence of peritoneal effusion, incidence of abdominal and pulmonary infections, retention time of abdominal drainage tube, postoperative bleeding incidence, second surgery rate, postoperative hospital stay, and postoperative mortality rate.

The retention time of the abdominal drainage tube is defined as the duration for which the longest-lasting drainage tube remains in place when multiple drainage tubes are used. The diagnosis of POPF is based on the definition of the International Study Group of Pancreatic Surgery (ISGPS)[8]. Grade A POPF is characterized by a drainage fluid amylase level exceeding three times the upper limit of serum amylase. Grade A POPF is also called "biochemical leak" (BL), which does not require treatment. Grade B POPF is defined as the occurrence of severe complications on the basis of BL, requiring a change in the postoperative management (abdominal drainage tube retention time > 3 weeks). Grade C POPF refers to the failure of one or several organs that require reoperation and/or death due to surgery-related complications. The diagnosis of DGE is based on the ISGPS guidelines released in 2007[9], which is defined as patients who need nasogastric tube retention for more than 7 days postoperatively, or require long-term enteral nutrition.

Surgical procedure

Before performing the MP surgery, all patients underwent laboratory tests and imaging examinations. MP surgery was performed only if experienced physicians judged that there was a high likelihood of a non-invasive lesion. Anesthesia was administered using a combination of intravenous and inhalation anesthesia. Once surgery began, the gastrocolic ligament at the upper edge of the transverse colon mesentery was incised with an ultrasonic scalpel, and the adhesions were carefully separated to examine the pancreatic neck and pancreatic body where the mass was located. To better expose the superior mesenteric vein, a combination of frontal and lateral approaches was used. The space between the pancreatic neck and the portal vein was carefully separated, followed by the upper and lower margins of the pancreas. In the area behind the left side of the mass, the superior mesenteric vein and the splenic vein were isolated and exposed. The pancreas was cut approximately 1 cm from the left side of the mass using an ultrasonic scalpel, and the main pancreatic duct was examined. The right pancreatic stump was lifted and then separated along the surface of the superior mesenteric vein and the portal vein towards the right side. The right branch of the portal vein was closed with a Hem-o-lok clip and then cut. Around 1 cm from the right side of the mass, the pancreatic head tissue was bundle-clipped and severed, allowing the mass and part of the pancreatic tissue to be removed entirely. If intraoperative pathology report revealed a non-invasive lesion, a pancreatojejunostomy was performed. However, if it indicated malignancy, distal pancreatectomy and abdominal lymph node dissection were performed. Figure 1 shows a schematic diagram of pancreatic mass resection.

For the IMPD-J bridge drainage procedure, the steps are as follows: First, a silicone drainage tube was selected according to the diameter of the main pancreatic duct (approximately 20-30 cm in length). A No. 4 suture was tied 2-3 cm from one end of the drainage tube. As shown in Figure 2, this knotted end was then inserted into the main pancreatic duct. A U-shaped suture was then placed on the pancreatic stump using 4-0 polypropylene non-absorbable suture (PROLENE® Polypropylene Suture). Before tightening the knot, the suture tied to the pancreatic duct was interlocked with the U-shaped suture, securing the drainage tube to the upper and lower edges of the pancreas. The other end of the drainage tube was then passed through the transverse mesocolon and into the jejunum approximately 10-15 cm below the

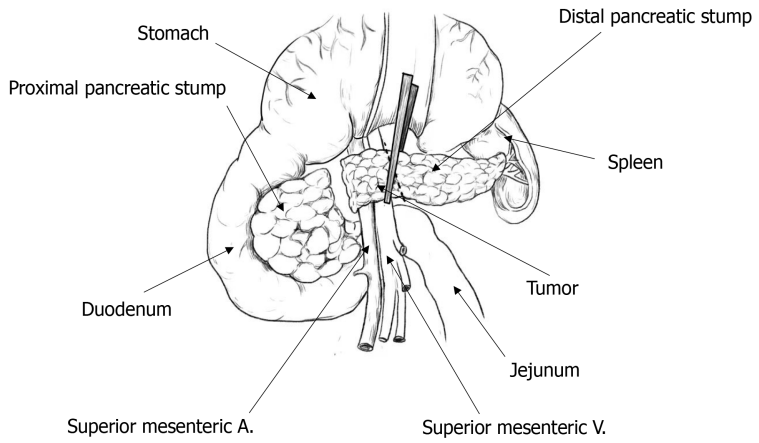

Figure 1 Schematic diagram of pancreatic mass resection. A: Artery; V: Vein.

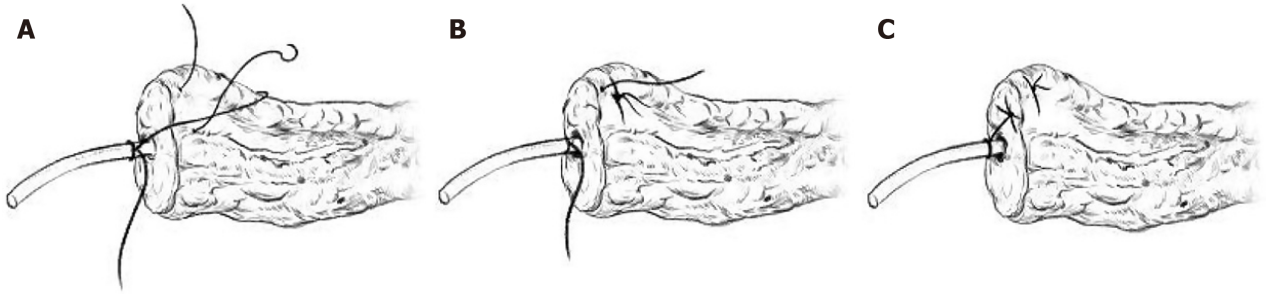

Figure 2 Schematic diagram of the interlocking fixation of the drainage tube. A: A silicone drainage tube tied with suture is placed into the main pancreatic duct. Another suture is inserted through the surface of the pancreas and exited from the section, then go the other way, namely U-shaped stitch; B: Tie the two sutures separately; C: Tightening the knot and cutting off the excess, and complete the interlocking fixation.

ligament of Treitz. After ensuring that there is no tension at the anastomosis, suture and embed to secure the suture on the intestinal side to the drainage tube. Barbed suture was used to create a submucosal tunnel within the intestinal wall to embed the drainage tube, ensuring both the pancreatic end and the intestinal end of the tube are securely fixed. Figure 3 shows clinical photographs that depict the step-by-step process of the bridge drainage procedure. Figure 4 demonstrates the application of IMPD-J bridge drainage for MP.

The surgical procedure for duct-to-mucosa pancreaticojejunostomy is as follows: First, the main pancreatic duct was located, and a suitable silicone drainage tube was chosen based on the duct's diameter and carefully inserted into the duct. Next, in the lower section of the colon, the jejunal mesentery was incised, and the jejunum was cut about 15 cm away from the ligament of Treitz. The distal end was closed with size 0 sutures, and the stump was sutured. The proximal end was prepared for anastomosis with the pancreas. An incision was then made in the avascular region of the transverse mesocolon, and the distal jejunal loop was pulled into the upper section of the colon. Subsequently, a small incision, approximately 3 mm in diameter, was made in the distal jejunal loop using an electrocautery hook to expose the mucosal layer. The main pancreatic duct was mobilized by 1 to 2 cm. Starting from the posterior wall, 4-0 polydioxanone absorbable sutures were used to anastomose the main pancreatic duct to the jejunal mucosa (6-8 stitches). This suturing process ensured a tight, tension-free, and leak-proof connection. The final step involved creating an end-to-side anastomosis between the proximal and distal jejunal loops, about 20 cm away from the pancreaticojejunal anastomosis. The diameter of the anastomosis was approximately 2 cm, ensuring it remains open and without leakage. Figure 5 shows the schematic diagram of traditional duct-to-mucosa pancreaticojejunostomy used in MP. Following the completion of the anastomosis, the abdominal cavity was irrigated with warm saline to remove any residual debris and ensure a clean environment. After confirming that there was no bleeding, a flushable drainage tube was placed near the pancreatic section, with Venturi foramens to aid in drainage and reduce the risk of fluid accumulation. Once the drainage tube was in place, the abdomen was closed securely to complete the procedure.

Post-operative management

For postoperative care following pancreatic surgery, routine treatments included hemostasis, pain relief, fluid replacement, anti-inflammatory medication, acid suppression, nebulization, and parenteral nutrition. After removing the nasogastric tube, patients were allowed to eat orally. Amylase levels in the drainage fluid were measured daily, and the required volume of saline for flushing was adjusted based on measured levels. If the amylase levels in the drainage fluid was below 100 U/L for two consecutive tests, the abdominal drainage tube could be removed. If DGE, abdominal fluid accumulation, intra-abdominal or thoracic infections, post-pancreatectomy hemorrhage, or other serious complications

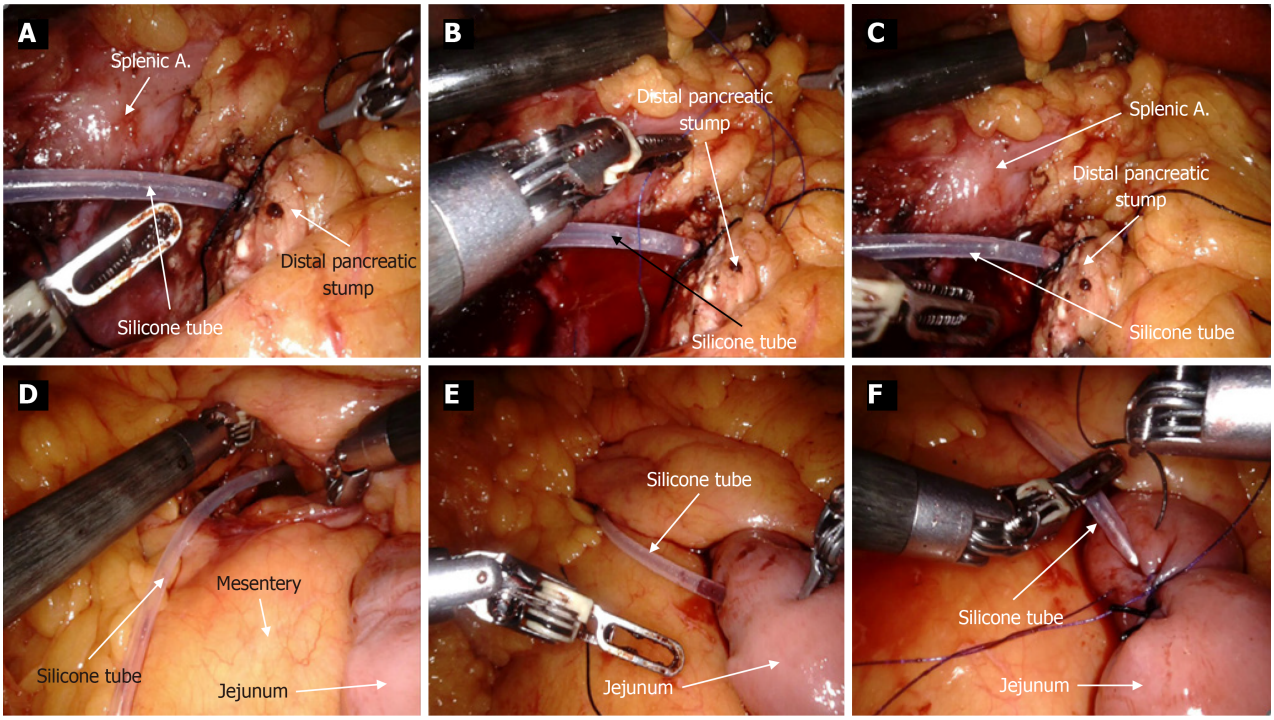

Figure 3 Clinical photographs depicting the step-by-step process of the bridge drainage procedure. A: Tie a suture around the surface of the drainage tube and then insert it into the main pancreatic duct; B: Use 4-0 polypropylene non-absorbable suture to create a U-shaped stitch; C: Secure the Prolene suture and the tied suture together in an interlocking manner; D: Pass the other side of the drainage tube through the transverse mesocolon; E: Pass through the transverse mesocolon and into the jejunum approximately 10-15 cm below the ligament of Treitz; F: Secure and embed the drainage tube using barbed sutures. A: Artery.

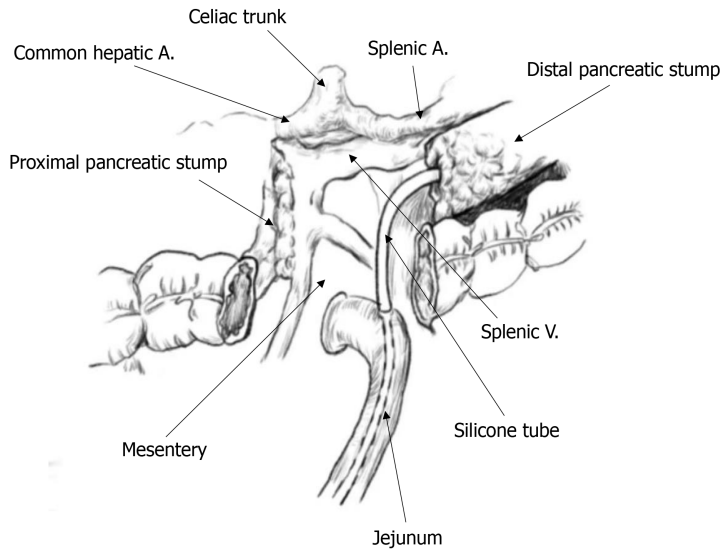

Figure 4 Illustration of the application of interlocking main pancreatic duct-jejunal bridge drainage for middle pancreatectomy. A: Artery; V: Vein.

were suspected, further examinations were performed, such as computed tomography or ultrasound examinations. If necessary, endoscopic procedures, interventional treatments, or a second surgery could be performed.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0. Statistical significance is defined as a two-sided $P < 0.05$. All data underwent the single-sample Kolmogorov-Smirnov (K-S) test to determine whether they conformed to a normal distribution. Continuous data with normal distribution are presented as mean ± SD, and differences between groups are examined using *t*-tests. Continuous data without normal distribution are presented with median and interquartile range, and differences between groups are examined using Mann-Whitney *U* test. Categorical data are presented as number and

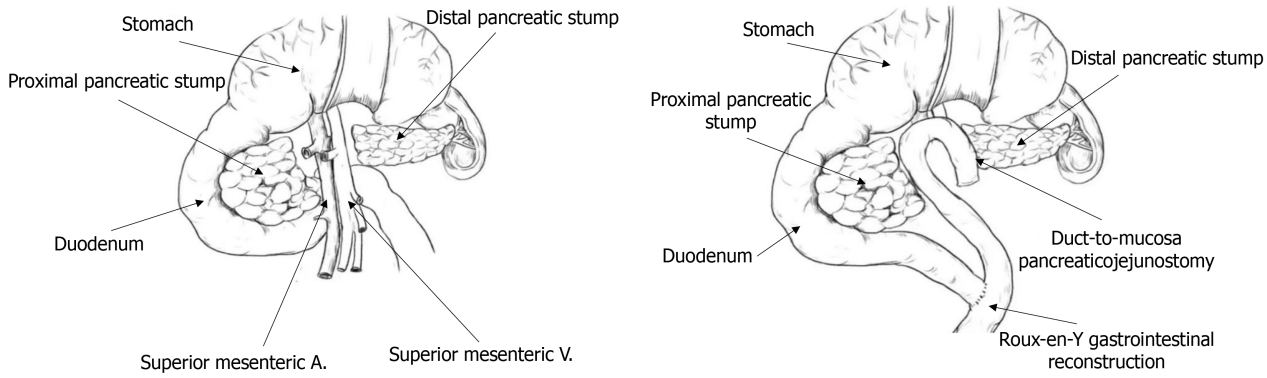

Figure 5 Schematic diagram of traditional duct-to-mucosa pancreaticojejunostomy used in mid-pancreatectomy. A: Artery; V: Vein.

percentage, and differences between groups are tested using χ^2-tests or Fisher's exact test. Binary logistic regression analysis was employed to identify risk factors associated with CR-POPF. Risk factors with a P value < 0.1 in univariate analysis were included in the binary logistic regression model for multivariate analysis. Factors with a P value < 0.05 were considered as independent risk factor for CR-POPF.

RESULTS

Demographics and patient characteristics

A total of 54 patients were enrolled in this study, including 23 patients in the IMPD-J bridge drainage group and 30 patients in the traditional duct-to-mucosa pancreaticojejunostomy group. Table 1 shows the demographics and patient characteristics of the two groups. There were no statistical differences between the two groups in terms of gender, age, BMI, smoking history, alcohol consumption history, hypertension, diabetes, and preoperative laboratory parameters (P > 0.05).

Comparison of the intraoperative and postoperative outcomes

Table 2 shows the intraoperative data of patients in the two groups. There were no significant differences between the two groups in terms of intraoperative blood loss red blood cells, intraoperative plasma transfusion, tumor diameters, and pancreatic duct diameters (P > 0.05). However, IMPD-J bridge drainage group had a significant shorter operation time than traditional duct-to-mucosa pancreaticojejunostomy group (4.3 ± 1.3 hours *vs* 5.8 ± 1.8 hours, P = 0.002). Regarding to the postoperative outcomes (Table 3), IMPD-J bridge drainage group had a significantly shorter nasogastric tube retention days than traditional duct-to-mucosa pancreaticojejunostomy group (5.3 ± 1.7 days *vs* 6.5 ± 2.0 days, P = 0.031), lower incidence of DGE (8.7% *vs* 36.7%, P = 0.019), and lower incidence of CR-POPF (39.1% *vs* 70.0%, P = 0.025). No differences were observed between groups with regards to postoperative body temperature (> 38.5 °C), blood-borne infection, drainage tube infection, peritoneal effusion, postoperative bleeding, interventional/endoscopic treatment, intubation time, and length of hospital stay (P > 0.05).

Independent risk factors for clinically relevant pancreatic fistula

Univariable binary logistic regression analysis was used to identify the unique characteristics associated with the CR-POPF. As shown in Table 4, type of pancreaticojejunostomy and plasma prealbumin content were potential influencing factors for the occurrence of CR-POPF. Multivariate logistic regression analysis further confirmed that type of pancreaticojejunostomy (odds ratio = 4.219, 95% confidence interval = 1.238-14.379, P = 0.021) and plasma prealbumin content (odds ratio = 1.132, 95% confidence interval = 1.001-1.281, P = 0.049) were independent risk factor for the occurrence of CR-POPF (Table 5). This result suggests that the risk of CR-POPF in MP patients who underwent traditional duct-to-mucosa pancreaticojejunostomy is 4.219 times higher than those who underwent IMPD-J bridge drainage.

Safety

Patients were followed up until July 31, 2023. In the IMPD-J bridge drainage group, 18 patients were follow-up, with durations ranging from 4 to 65 months. Among these patients, 13 did not experience recurrent abdominal pain, back pain, steatorrhea, fever, pancreatitis, pseudocysts, or significant weight loss after discharge. Two patients occasionally experienced mild discomfort in the upper abdomen and back, but laboratory indicators and imaging examinations showed that there was no pancreatitis or pseudocyst. One patient experienced recurrence of pancreatitis (no pseudocyst). In addition, the patient reported decreased tolerance to alcohol, and was prone to experience upper abdominal and back pain after drinking. A 64-year-old patient with atypical adenomatous hyperplasia was discharged on the 9th postoperative day, but was readmitted 4 months later due to jaundice. Image examinations revealed local recurrence with extensive peritoneal lymph node metastasis. Carbohydrate antigen 19-9 levels increased to 47.6 U/mL (normal: 0-37 U/mL). This patient was discharged after completing one round of chemotherapy and was subsequently lost to follow-up. Out of the

Table 1 Demographics and patient characteristics of the study cohort

	IMPD-J bridge drainage (*n* = 23)	Duct-to-mucosa pancreaticojejunostomy (*n* = 30)	χ^2/*t*/*z*	*P* value
Age, years, *n* (%)	57.0 (52.0, 64.0)	61.0 (51.0, 67.0)	0.944	0.345
Male, *n* (%)	12 (52.2)	15 (50.0)	0.025	0.875
Female, *n* (%)	11 (47.8)	15 (50.0)		
BMI, kg/m^2	23.2 (20.4, 24.6)	22.2 (19.6, 23.4)	-1.212	0.225
Smoking, *n* (%)	7 (30.4)	15 (50.0)	2.053	0.152
Alcohol consumption, *n* (%)	7 (30.4)	4 (13.3)	2.315	0.128
Hypertension, *n* (%)	5 (21.7)	8 (26.6)	0.171	0.679
Diabetes, *n* (%)	10 (43.5)	7 (23.3)	2.425	0.119
WBC, 10^9/L	5.3 (4.7, 5.8)	5.0 (4.9, 6.1)	0.117	0.907
Neutrophils, 10^9/L	2.8 (2.5, 3.1)	3.0 (2.6, 3.6)	0.808	0.419
Platelet, 10^9/L	224.7 ± 63.1	198.3 ± 55.3	1.619	0.112
Albumin, g/L	42.6 ± 3.9	41.9 ± 3.8	0.480	0.633
Prealbumin, mg/dL	20 ± 10	20 ± 10	0.03	0.977
Total bilirubin, μmol/L	11.4 (6.7, 15.9)	11.4 (10.1, 14.5)	0.188	0.851

IMPD-J: Interlocking main pancreatic duct-jejunal; BMI: Body mass index; WBC: White blood cells.

Table 2 Intraoperative data of patients who underwent interlocking main pancreatic duct-jejunal bridge drainage or duct-to-mucosa pancreaticojejunostomy

	IMPD-J bridge drainage (*n* = 23)	Duct-to-mucosa pancreaticojejunostomy (*n* = 30)	χ^2/*t*/*z*	*P* value
Operation time, hours	4.3 ± 1.3	5.8 ± 1.8	-3.233	0.002
Blood loss, mL	100.0 (50.0, 200.0)	100.0 (87.5, 300.0)	-1.894	0.058
RBC transfusion, u	0 (0, 0)	0 (0, 0)	-0.197	0.843
Plasma transfusion, mL	0 (0, 0)	0 (0, 75.0)	-0.507	0.612
Tumor diameter, cm	4.1 ± 2.3	3.9 ± 1.9	0.303	0.763
Pancreatic duct diameter, mm	3.0 (3.0, 5.0)	3.0 (2.4, 6.0)	-2.420	0.809

IMPD-J: Interlocking main pancreatic duct-jejunal; RBC: Red blood cells.

18 patients, only one experienced recurrent pancreatitis accompanied by steatorrhea and lost 30 kg in body weight within 5 months, without developing diabetes. Subsequent endoscopic ultrasound revealed significant dilation at the distal end of the main pancreatic duct, where a silicone tube was inserted. It is speculated that the silicone tube was too large, causing overexpansion and damage to the duct, eventually leading to recurrent pancreatitis. This patient underwent a second surgery 6 months after the operation. After the silicone tube was removed, the symptoms of pancreatitis disappeared without recurrence.

DISCUSSION

Since the first case of MP was performed in 1957, its application has expanded from chronic pancreatitis to non-invasive tumors in the neck and body of the pancreas, with intraductal papillary mucinous neoplasms and pancreatic neuroendocrine tumors being the most commonly treated tumors. Currently, most researchers believe that compared to traditional Whipple surgery and distal pancreatectomy, MP, while preserving pancreatic function, is more likely to cause one or more perioperative complications. Klotz *et al*[10] found that patients undergoing MP were more likely to experience abdominal bleeding, although it did not lead to more severe outcomes such as CR-POPF and an extended hospital stay. Studies by Regmi *et al*[11] and Asano *et al*[12] suggested that the incidence of CR-POPF is higher in MP compared to traditional pancreatic surgeries. This observation is not surprising, as MP leaves two pancreatic stumps after

Table 3 Postoperative outcomes of patients who underwent interlocking main pancreatic duct-jejunal bridge drainage or duct-to-mucosa pancreaticojejunostomy

	IMPD-J bridge drainage (*n* = 23)	Duct-to-mucosa pancreaticojejunostomy (*n* = 30)	$\chi^2/t/z$	*P* value
Temperature > 38.5 °C, *n* (%)	5 (21.7)	5 (16.7)	0.013	0.910
Blood culture (positive), *n* (%)	0 (0)	2 (6.7)	NA	0.499
Drainage tube infection, *n* (%)	4 (17.4)	4 (13.3)	NA	0.715
Nasogastric tube retention, days	5.3 ± 1.7	6.5 ± 2.0	-2.218	0.031
DGE, *n* (%)	2 (8.7)	11 (36.7)	5.502	0.019
Peritoneal effusion, *n* (%)	1 (4.4)	6 (20.0)	2.782	0.095
Intervention/endoscopic treatment, *n* (%)	0 (0)	1 (3.3)	NA	1.000
Postoperative bleeding, *n* (%)	1 (4.4)	1 (3.3)	NA	1.000
Length of hospital stay, days	24.0 (14.0, 29.0)	29 (9.8, 40.3)	-0.844	0.399
Drainage tube retention time, days	20.0 (13.0, 36.0)	27 (17.8, 40.0)	-1.096	0.273
POPF 0, *n* (%)	6 (26.1)	5 (16.7)	NA	NA
A, *n* (%)	8 (34.8)	4 (13.3)	NA	NA
B, *n* (%)	8 (34.8)	21 (70.0)	NA	NA
C, *n* (%)	1 (4.4)	0 (0)	NA	NA
CR-POPF, *n* (%)	9 (39.1)	21 (70.0)	5.051	0.025

IMPD-J: Interlocking main pancreatic duct-jejunal; NA: Not available; DGE: Delayed gastric emptying; POPF: Postoperative pancreatic fistula; CR-POPF: Clinically relevant postoperative pancreatic fistula.

surgery, increasing the likelihood of pancreatic fluid leakage into the abdominal cavity[13]. Clinically, the proximal pancreatic stump can be closed directly using a right-angle cutter or sutured manually after ultrasonic dissection. However, managing the distal pancreatic stump is challenging. If it is closed off like the proximal pancreatic stump, pancreatic fluid won't be able to escape, increasing the risk of pancreatitis and reducing the preservation of pancreatic function. Therefore, pancreatojejunostomy and pancreatogastrostomy are two common surgical methods for the management of distal pancreatic stump. Although there's no clear consensus on which anastomotic method is preferable [14], a long-term analysis of residual pancreatic function indicated that pancreatogastrostomy may impair long-term exocrine pancreatic function due to excessive growth of gastric mucosa[15]. In the treatment experience of our team, we tend to use pancreaticojejunostomy, and IMPD-J bridge drainage is also an improvement based on the traditional duct-to-mucosa pancreaticojejunostomy.

IMPD-J bridge drainage is a relatively novel anastomotic technique originally developed to manage a pancreaticojejunostomy leak in a patient after Whipple surgery. The severe dehiscence of the original anastomosis, coupled with significant edema, rendered re-anastomosis unfeasible. Additionally, the patient's advanced age and severe infection further reduced the likelihood of a successful re-anastomosis. Under these challenging circumstances, our surgical team resorted to this innovative approach. Remarkably, the patient's recovery was unexpectedly smooth, leading to discharge 34 days after re-surgery. During the subsequent 27 months of follow-up, no postoperative complications such as diabetes or pseudocysts were observed.

The results from this study further confirm the advantages of applying IMPD-J bridge drainage in MP, with a mean operating time of 4.3 ± 1.3 hours, which significantly shorter than the 5.8 ± 1.8 hours of the traditional duct-to-mucosa pancreaticojejunostomy ($P < 0.05$). This notable difference in operating time could offer greater flexibility for the surgical team and benefit the patients. In addition, compared to the conventional duct-to-mucosa anastomosis, the key feature of IMPD-J bridge drainage is that it doesn't require direct anastomosis between the main pancreatic duct and the intestinal mucosa. Instead, it uses a silicone tube as a "bridge" to transport pancreatic fluid. This design reduces the risk of leakage that might occur with traditional anastomosis, thereby decreasing the likelihood of postoperative complications. Of note, the digestive tract does not require Roux-en-Y reconstruction. These findings suggest that IMPD-J bridge drainage not only shortens operating time by simplifying the surgical steps, but also effectively lowers the risk of postoperative complications. For robotic or laparoscopic surgery, the complexity of robotic arm operations and the separation between hand and eye movements further highlight the clinical applicability of this method that simplify surgical procedures.

The study found that compared to patients who underwent traditional duct-to-mucosa pancreaticojejunostomy, patients who underwent IMPD-J bridge drainage had significantly lower nasogastric tube retention time (5.3 ± 1.7 days *vs* 6.5 ± 2.0 days, $P < 0.05$) and lower risk of DGE (8.7% *vs* 36.7%, $P < 0.05$), which could be attributed to the fact that IMPD-J bridge drainage does not require Roux-en-Y digestive tract reconstruction. Although Roux-en-Y reconstruction is

Table 4 Univariable binary logistic regression analysis of potential influencing factors for the occurrence of clinically relevant postoperative pancreatic fistula

	OR	95%CI	*P* value
Age, year	0.971	(0.925, 1.019)	0.229
Gender (ref: Male)	2.034	(0.673, 6.146)	0.208
BMI, kg/m^2	1.508	(0.891, 1.257)	0.517
Smoking	0.632	(0.209, 1.907)	0.415
Alcohol consumption	0.567	(0.149, 2.158)	0.405
Diabetes	0.396	(0.121, 1.289)	0.124
Hypertension	0.862	(0.245, 3.003)	0.817
WBC	0.719	(0.439, 1.715)	0.188
Platelet	0.999	(0.990, 1.009)	0.912
Albumin	1.115	(0.956, 1.301)	0.166
Prealbumin	1.111	(0.994, 1.242)	0.063
Total bilirubin	0.911	(0.801, 1.307)	0.158
Operation type (ref: IMPD-J bridge drainage)	3.630	(1.155, 11.406)	0.027
Tumor diameter	0.908	(0.697, 1.183)	0.475
Pancreatic duct diameter	0.912	(0.707, 1.176)	0.477
Bleeding	1.002	(0.999, 1.006)	0.218
Blood transfusion	1.102	(0.665, 1.827)	0.706
Plasma transfusion	1.000	(0.998, 1.002)	0.943

OR: Odds ratios; CI: Confidence interval; BMI: Body mass index; WBC: White blood cells; IMPD-J: Interlocking main pancreatic duct-jejunal.

Table 5 Multivariate logistic regression analysis of independent risk factors for the occurrence of clinically relevant postoperative pancreatic fistula

	OR	95%CI	*P* value
Operation type (ref: IMPD-J bridge drainage)	4.219	(1.238, 14.379)	0.021
Prealbumin	1.132	(1.001, 1.281)	0.049

OR: Odds ratios; CI: Confidence interval; IMPD-J: Interlocking main pancreatic duct-jejunal.

generally considered safe[16,17], it still disrupts the physiological integrity of the digestive tract. In contrast, the operation of IMPD-J bridge drainage only requires a small incision in the jejunum, embedding and fixing a silicone drainage tube using barbed sutures, thereby maintaining the integrity of the digestive tract to a certain extent. Only two patients had to continue using the nasogastric tube due to nausea and gastroesophageal reflux after removal of the tube. However, both patients also had successful nasogastric tube removal on the eighth postoperative day and were able to eat orally. By contrast, among patients who underwent traditional duct-to-mucosa pancreaticojejunostomy, 11 cases of DGE occurred, with three requiring nasogastric tubes for up to 10 days. These findings clearly show that IMPD-J bridge drainage surgery has advantages in terms of shorter nasogastric tube retention time and lower DGE incidence.

Regarding POPF, this study found that IMPD-J bridge drainage had significantly lower incidence of CR-POPF compared to duct-to-mucosa pancreaticojejunostomy (39.1% *vs* 70.0%, $P < 0.05$). According to the latest 2016 ISGPS criteria for POPF, 17 patients in the IMPD-J bridge drainage group developed POPF. Among them, 8 had grade A POPF, manifested by elevated amylase levels in the drainage fluid on the third day after operation (no further management required). Two patients experienced stress-induced hyperthermia, with the highest recorded temperature being 38.6 °C - one on the first day and the other on the ninth day. Blood and drainage fluid cultures taken during the fever episodes were negative for bacterial growth. The patient with fever on the first day after surgery had an increase in WBCs to 16 × 10^9/L, which may be related to the surgery. For the patient who had a fever on the ninth day after operation, the number of WBCs did not increase. Both patients' temperatures returned to normal within 24 hours without any change in the type or dosage of antibiotics, relying solely on physical cooling. Therefore, these two people were not classified as CR-POPF. A

total of 9 patients developed CR-POPF, 8 of whom were grade B POPF, mainly manifested by elevated amylase levels in the drainage fluid, and the mean drainage tube retention time was more than 21 days (the longest retention time was 106 days). Among these 8 patients, 3 experienced chills and high fever, with 2 having positive bacterial cultures from abdominal drainage fluid, while the third had unknown infection sources (both abdominal drainage fluid and blood cultures testing negative). Nonetheless, the source of the infection was deduced to be from the drainage tube, because the patient's abdominal computed tomography scan on the day of fever suggested increased fluid leakage in the surgical area. In addition, 2 of the 8 patients with grade B POPF did not develop symptoms such as chills and high fever, but the bacterial culture of the drainage fluid was positive on the 14th and 13th days postoperative days, and they were accompanied by a rapid increase in WBCs. Only one patient was classified as grade C POPF because of abdominal bleeding on the second postoperative day and the bleeding was immediately stopped during laparotomy. It was found that a local hematoma had formed, with a volume of approximately 300 mL. The bleeding site was located at the incision surface of the proximal residual pancreas, but not at the pancreaticojejunostomy, distal remnant pancreas, and splenic artery and vein. The cause of the bleeding is suspected to be either a slipped suture or the rupture of an electrocautery hemostasis point. However, since the amylase level had reached 3200 U/L at the time of the bleeding, the possibility of bleeding caused by local blood vessel erosion due to pancreatic fluid leakage cannot be completely ruled out.

In comparison, duct-to-mucosa pancreaticojejunostomy had a higher incidence of POPF. Out of 30 patients, 25 developed POPF, with only 4 having grade A POPF, while the remaining 21 were classified as grade B POPF due to complications such as disease progression, intra-abdominal bleeding, interventional treatment, or long-term drainage. The longest drainage time was 96 days, experienced by a 33-year-old male who underwent a MP for a solid pseudo-papillary tumor. This patient had two abdominal drains placed postoperatively, one at the Winslow's foramen and one at the pancreatic transection site. The drainage tube placed at Winslow's foramen was kept in place for up to 17 days because of elevated amylase levels in the drainage fluid near the transection site, which caused by persistent pancreatic fluid leakage. Even with daily irrigation with saline, white flocculent material continued to form. In addition, prolonged pancreatic fluid leakage resulted in pancreatic fluid collection at the transection site. The patient underwent ultrasound-guided thoracentesis and abdominal puncture 48 days after the operation and then discharged from the hospital with a drainage tube in place 78 days after the operation. The tube was removed during a follow-up visit on the 96th day. This patient's prolonged drainage may be attributable to severe obesity, as the patient had a preoperative BMI of 37.04, although there was no history of diabetes or alcohol consumption. Among the 21 patients with grade B POPF, 5 experienced chills and high fever, requiring an escalation in antibiotic treatment. The bacterial culture of abdominal drainage fluid of 3 people was positive. The other 2 had unknown sources of infection, with negative results for both drainage fluid and blood cultures, and no evidence of pancreatic fluid collection on imaging. They only showed clinical symptoms and increased WBC counts. Among the patients with normal body temperature after surgery, one patient's drainage fluid bacterial culture was positive, but the WBC count did not increase significantly. Since this patient had no clinical symptoms, no treatment was administered; instead, the situation was closely monitored. The patient's abdominal drainage tube was removed 40 days after operation, without any evidence of abdominal effusion.

Traditional duct-to-mucosa pancreatojejunostomy involves creating an anastomosis between the main pancreatic duct and the jejunal mucosa. If using too few stitches during suturing, gaps may form between the pancreatic duct and the jejunal mucosa, potentially leading to leakage. Although too many stitches can ensure a tight enough anastomosis, it will also increase the risk of damage to the pancreatic duct and the intestinal mucosa. In particular, the use of multiple stitches is more likely to aggravate the damage to capillaries at the anastomotic site, greatly increasing the risk of POPF. Studies have shown that inadequate blood supply at the anastomotic site is more likely to cause delayed healing or even ischemic necrosis[18,19]. The emergence of IMPD-J bridge drainage offers a solution to this problem. While the silicone tube acting as a bridge is fixed to the main pancreatic duct, the suture needle only needs to penetrate the pancreatic parenchyma. During the subsequent anastomosis, there is no need to insert a needle from the main pancreatic duct, which reduced the risk of damage to the main pancreatic duct. On the other hand, enterokinase secreted by the small intestine can activate trypsinogen. If the main pancreatic duct is directly anastomosed to the jejunum, pancreatic juice will be quickly activated by enterokinase as soon as it enters the jejunum, which can lead to erosion at the anastomosis site. The advantage of the IMPD-J bridge drainage is demonstrated here. It can drain pancreatic juice to a location further away from the anastomosis site. This means that even if trypsinogen is activated, it won't directly contact the anastomosis site, lowering the risk of POPF.

When IMPD-J bridge drainage was initially applied in three patients with anastomotic dehiscence, several steel beads were placed inside the silicone tube, and absorbable sutures were used to secure the silicone tube to the pancreas. After a few months, the steel beads' weight would cause the silicone tube to fall off, enter the intestinal tract, and be expelled from the body. During this period, pancreatic duct epithelial cells would grow along the silicone tube to the anastomotic site, wrap around the omentum, and subsequently form sinus tracts locally. This prevented pancreatic fluid leakage even after the silicone tube had detached. The three patients expelled the silicone tube at 67, 180, and 92 days after operation, respectively. During subsequent follow-ups, ranging from 5 to 27 months, no pancreatitis, pancreatic fluid leakage, or pseudocysts were observed. The original intention of this approach is to consider that was based on the fact that silicone is a foreign material. Although it is highly resistant to corrosion, long-term retention could potentially lead to rejection, recurrent inflammation, repeated infections, organ adhesions, and pseudocyst formation. However, with advances in medical devices and improved healthcare practices, silicone is now considered a relatively safe material and is widely used in prosthetics and patches. Therefore, in later IMPD-J bridge drainage procedures, the placement of steel beads to ensure silicone tube detachment was deemed unnecessary. The focus shifted to securing the silicone tube between the pancreas and the jejunum to reduce perioperative pancreatic fluid leakage and the risk of POPF. For this reason, non-absorbable sutures were used to fix the silicone tube to the pancreas.

Our IMPD-J bridge drainage procedure has some similarities to the modified MP procedure developed by Liu and Zhao[20] in 2018. Here's a brief introduction to the procedure. According to Liu and Zhao[20], when the main pancreatic duct resection is less than 5 cm, the reconstruction involves a bridging repair of the main pancreatic duct plus an end-to-end pancreatic anastomosis. In this approach, a silicone tube is inserted into the main pancreatic duct and fixed with absorbable sutures. The two ends of the pancreatic remnant are then brought together and sutured with non-absorbable stitches. However, if the resection is more than 5 cm, bridging repair of the main pancreatic duct plus pancreatic stent exclusion are used, where the silicone tube is left in the main duct to facilitate pancreatic fluid drainage. Compared to our IMPD-J bridge drainage approach, the key differences are: (1) This method reconstructs the main pancreatic duct between the proximal and distal residual pancreas without performing pancreaticojejunostomy; and (2) The silicone tube is always fixed to the pancreas using absorbable sutures, allowing for eventual expulsion after a few months. In this approach, 13 patients developed POPF, mostly grade BL and grade B, with drainage times ranging from 13 days to 10 months, and no formation of pancreatic-cutaneous fistulas. In follow-up over 1 to 16 months, three patients did not expel the silicone tube. However, this report did not discuss the long-term effects of having an externally implanted silicone tube in the pancreatic duct. According to the results from our follow-up, most tolerated the intra-abdominally placed silicone tube well. Only one patient experienced recurrent pancreatitis due to the large diameter of the silicone tube and had it removed six months after surgery. The silicone tubes in the remaining patients were well-secured. Therefore, from a long-term perspective, our IMPD-J bridge drainage approach appears to be a feasible approach.

This study has a few limitations. First, it is a single-center retrospective study with a limited sample size. Second, the time period between cases was too long, and some patients were lost to follow-up. Third, although IMPD-J bridge drainage could shorten the operation time, there is a lack of data on pancreaticojejunostomy time in the medical records, making further analysis not possible. Therefore, in subsequent studies, it would be important to separately record the overall surgical time and the time taken for pancreatojejunostomy. Lastly, this study only compared IMPD-J bridge drainage with traditional duct-to-mucosa pancreatojejunostomy. To further validate its safety and simplicity, comparisons with other surgical approaches would be helpful.

CONCLUSION

IMPD-J bridge drainage is easy to perform, with the advantages of shorter operation time, lower risk of CR-POPF and DGE, and long-term safety. It is a suitable technique for MP procedures.

FOOTNOTES

Author contributions: Lu XY and Tan XD conceptualized and designed this study; Lu XY contributed to data acquisition, data analysis, data interpretation, and manuscript drafting; Tan XD revised the manuscript critically for important intellectual content and supervised the study; and all authors read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Successful management of bleeding ectopic small bowel varices secondary to portal hypertension: A retrospective study

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Abstract

BACKGROUND

Bleeding ectopic varices located in the small bowel (BEV-SB) caused by portal hypertension (PH) are rare and life-threatening clinical scenarios. The current management of BEV-SB is unsatisfactory. This retrospective study analyzed four cases of BEV-SB caused by PH and detailed the management of these cases using enteroscopic injection sclerotherapy (EIS) and subsequent interventional radiology (IR).

AIM

To analyze the management of BEV-SB caused by PH and develop a treatment algorithm.

METHODS

This was a single tertiary care center before-after study, including four patients diagnosed with BEV-SB secondary to PH between January 2019 and December 2023 in the Air Force Medical Center. A retrospective review of the medical records was conducted. The management of these four patients involved the utilization of EIS followed by IR. The management duration of BEV-SB in each patient can be retrospectively divided into three phases based on these two approaches: Phase 1, from the initial occurrence of BEV-SB to the initial EIS; phase 2, from the initial EIS to the initial IR treatment; and phase 3, from the initial IR to December 2023. Descriptive statistics were performed to clarify the blood transfusions in each phase.

RESULTS

Four out of 519 patients diagnosed with PH were identified as having BEV-SB. The management duration of each phase was 20 person-months, 42 person-months, and 77 person-months, respectively. The four patients received a total of eight and five person-times of EIS and IR treatment, respectively. All patients

exhibited recurrent gastrointestinal bleeding following the first EIS, while no further instances of gastrointestinal bleeding were observed after IR treatment. The transfusions administered during each phase were 34, 31, and 3.5 units of red blood cells, and 13 units, 14 units, and 1 unit of plasma, respectively.

CONCLUSION
EIS may be effective in achieving hemostasis for BEV-SB, but rebleeding is common, and IR aiming to reduce portal pressure gradient may lower the rebleeding rate.

Key Words: Suspected small bowel bleeding; Transjugular intrahepatic portosystemic shunt; Enteroscopic injection sclerotherapy; Bleeding ectopic varices; Portal hypertension

Core Tip: Bleeding ectopic varices located in the small bowel (BEV-SB) caused by portal hypertension is a rare, life-threatening clinical scenario. This retrospective study presented the treatment experience using enteroscopic injection sclerotherapy (EIS) and subsequent interventional radiology (IR) for BEV-SB. From January 2019 to December 2023, 4 of 519 patients with portal hypertension were identified as having BEV-SB. The management duration of phases from the first episode of BEV-SB to the first EIS, from the first EIS to the first IR, and from the first IR to December 2023 were 20 person-months, 42 person-months, and 77 person-months, respectively. The corresponding transfusions at each phase were 34 units, 31 units, and 3.5 units of red blood cells and 13 units, 14 units, and 1 unit of plasma, respectively. After the comprehensive management, no further gastrointestinal bleeding was observed. We conclude that EIS may be effective in achieving hemostasis in BEV-SB, although rebleeding is common, and IR aiming to reduce portal venous pressure may lower the rebleeding rate.

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INTRODUCTION

Ectopic varices (EV) are dilated portal-systemic collaterals that occur outside of the esophagus and stomach, and are usually presented as elevated submucosal tortuous vessels. Bleeding EV (BEV) can manifest as active bleeding or as clots, erosive spots, or ulcers without active bleeding. Small bowel varices, accounting for 0.6%-17% of all EV[1,2], are primarily caused by portal hypertension (PH) and can result in life-threatening hemorrhage with a mortality rate of up to 40%[2-4]. Despite numerous reported treatment strategies, outcomes for BEV in the small bowel (BEV-SB) have often been unsatisfactory[5]. Moreover, the scarcity of data on effective therapeutic modalities for BEV-SB hinders the conduct of large randomized controlled trials and precludes the identification of the ideal management approach for this rare condition [6]. In this before-after study, we retrospectively analyzed four patients who underwent both enteroscopic injection sclerotherapy (EIS) and interventional radiology (IR). The duration of BEV-SB treatment in each patient was retrospectively divided into three phases according to these two treatment approaches. From the before-after study, although there were only 4 cases, we speculate that EIS may be effective in achieving hemostasis in BEV-SB, but rebleeding is common, and IR, which aims to reduce the portal pressure gradient (PPG), may lower the rebleeding rate. This retrospective study may contribute to the preference of the IR option for BEV-SB caused by PH.

MATERIALS AND METHODS

We reviewed patients diagnosed with PH and BEV-SB at the Air Force Medical Centre between January 2019 and December 2023. Medical records and imaging data from the hospital information system and picture archiving and communication system were retrospectively collected for demographics, hemoglobin (Hb) concentration, transfusions, endoscopic treatment, and IR treatment. The management of these patients involved the utilization of EIS followed by IR, therefore a before-after study was designed. The management duration of BEV-SB in each patient was retrospectively divided into three phases based on these two approaches: (1) Phase 1, from the initial occurrence of BEV-SB to the initial EIS; (2) Phase 2, from the initial EIS to the initial IR treatment; and (3) Phase 3, from the initial IR to December 2023. Descriptive statistics were performed to clarify the blood transfusions in each phase. The local institutional review board approved the retrospective study (No. 2023-151-S01), and written informed consent was obtained from all patients.

RESULTS

Four out of the 519 patients diagnosed with PH were identified as having BEV-SB. The median age of these 4 patients at the first episode of BEV-SB was 47.5 years (range: 37 years to 58 years), with a 2:2 female-to-male ratio. In 3 patients, PH was caused by cirrhosis due to a history of hepatitis B, drug-induced liver injury, and alcoholic hepatitis, respectively. The fourth patient was diagnosed with regional PH resulting from splenic vein stenosis following acute pancreatitis. BEV-SB presented mainly as melena in two patients, one of whom concurrently experienced hematochezia during follow-up, and as hematochezia in the other two patients. The average Hb concentration at the first hospitalization was 72 g/L (range: 49 g/L to 85 g/L) and the Child-Pugh scores were 5, 6, 7, and 5, respectively.

The four patients were hospitalized 23 times during a total of 139 person-months of follow-up and received 68.5 units of red blood cells and 28 units of plasma transfusions. The duration and transfusions required for each phase for each patient are shown in Table 1. During phase 1, 17 conventional endoscopies (9 gastroscopies and 8 colonoscopies) were performed in the four patients, but no bleeding lesions were identified. However, all patients had esophageal varices. Although three patients underwent prophylactic endoscopic esophageal variceal ligation, the bleeding continued. For further investigation, three patients underwent enteroscopy, while one patient underwent capsule endoscopy, which indicated suspected BEV-SB, and subsequently underwent enteroscopy. During enteroscopy, BEV were located in the jejunum, 80 cm and 150 cm distal to the ligament of Treitz, and in the ileum, 40 cm and 100 cm distal to the ileocecal valve, respectively. The length of the varices ranged from approximately 6 cm to 15 cm with oozing or erosive lesions. After verifying the BEV-SB, we executed the first EIS for each patient (Figure 1), achieving temporary hemostasis in all patients.

However, the rebleeding occurred in 19 months, 4 months, 1 month, and 5 months after the first EIS, respectively. Patient 1 underwent two additional EIS, at 19 months and 32 months after the first EIS due to concurrent melena and hematochezia, and then accepted the transjugular intrahepatic portosystemic shunt (TIPS). Patients 2 and 3 directly underwent TIPS after achieving cessation of rebleeding with the second EIS. Patient 4 underwent splenic vein stent implantation (Figure 2) through the transjugular approach due to recurrent melena after the first EIS.

TIPS was performed on 3 cirrhotic patients with balloon dilation and metal stent implantation. The PPG was 30.5 mmHg, 37.5 mmHg, and 27.6 mmHg before TIPS, which decreased to 9.6 mmHg, 8.8 mmHg, and 10.3 mmHg after the procedure, respectively. However, patient 3 suffered rebleeding on the second day after TIPS, and an urgent IR was attempted, revealing acute shunt thrombosis. Another mental stent was then implanted, maintaining the PPG at 11.0 mmHg. In patient 4, the distal and proximal splenic vein pressures were 16.2 mmHg and 11.0 mmHg, respectively. Metal stents were implanted into the stenosis splenic vein, restoring pressure to 11.8 mmHg and 11.4 mmHg, respectively. During phase 3, there were 7 additional hospitalizations due to periodic follow-up visits, but no further gastrointestinal bleeding or other obvious complications were observed. At the last follow-up, the average Hb was 104.7 g/L (range: 86 g/L to 128 g/L).

DISCUSSION

Overt gastrointestinal bleeding is a common emergency that poses a significant challenge for clinicians. When conventional endoscopies like gastroscopy and colonoscopy fail to detect any bleeding lesions, the condition is known as "suspected small bowel bleeding" (SSBB). While BEV-SB is a rare cause of SSBB, advancements in diagnostic algorithms, enteroscopy, and capsule endoscopy have improved the diagnosis of this condition[7]. However, the treatment of BEV-SB remains a debated topic, with several strategies proposed, mainly including endoscopy, IR, and surgery. Unfortunately, an unsatisfactory prognosis is frequently encountered with this complex condition[5]. Moreover, due to the rarity of this disease and limited available data, determining the ideal management strategy for BEV-SB remains challenging.

Enteroscopy is considered a primary treatment for SSBB in selected patients given its potential therapeutic efficacy, ease of use, and tolerability[7]. EIS has been reported to be effective in managing BEV[8] and may have similar efficacy compared to enteroscopic cyanoacrylate injection[9]. Since enteroscopic band ligation is not available in our institution, we performed EIS with lauromacrogol injection (Polidocanol) as the first line therapy based on the endoscopist's clinical experiences. However, despite the efficient temporary hemostasis, as observed in our retrospective study, rebleeding of BEV-SB in the setting of PH can occur in 1-19 months in all patients after the first EIS. This is consistent with a single-center study where 86.7% of patients (13/15) achieved initial hemostasis by endoscopic treatment, but 53.3% (8/15) presented rebleeding[2]. Therefore, while EIS may serve as an option to control bleeding in the initial therapy, advanced treatment is required for BEV-SB with PH.

Reducing PPG through the IR approach is effective in managing BEV-SB. TIPS, which is designed for the decompression of PH, is associated with a relatively lower rebleeding rate[10], has been widely applied in patients with cirrhosis, and has also been recommended by guidelines[11,12]. For patients with prehepatic PH (non-cirrhosis) caused by stenosis or thrombosis of portal collaterals, recanalization may be the primary decompressive strategy if it is technically feasible[3]. Other IR approaches, such as percutaneous antegrade transhepatic venous obliteration or balloon-occluded retrograde transvenous obliteration, have also been used to treat BEV. In a case series of 12 patients treated by percutaneous antegrade transhepatic venous obliteration, the rebleeding rate is 50%[13]. In another case series of 6 patients treated by balloon-occluded retrograde transvenous obliteration, the rebleeding rate is 16.6%[14]. Additionally, as those obliteration therapies, in contrast to TIPS or recanalization, do not decrease the PPG, they can even worsen esophageal varices and ascites. Therefore, for patients with BEV-SB caused by PH, as shown in our study, IR with or without obliteration aimed at decompressing the PH is the first choice to reduce the risk of rebleeding.

Table 1 Durations and transfusions required for each phase of each patient

Patients	Phase 1 (first episode of BEV-SB to first EIS)		Phase 2 (first EIS to first IR)		Phase 3 (first IR to the December 2023)	
	Transfusions, RBC/P (units)	Duration, (months)	Transfusions, RBC/P (units)	Duration, (months)	Transfusions, RBC/P (units)	Duration, (months)
1	16/6	11	9.5/3	32	0/0	13
2	6/4	1	9/6	4	0/0	39
3	8/3	1	10.5/5	1	3.5/1	12
4	4/0	7	2/0	5	0/0	13
Total	34/13	20	31/14	42	3.5/1	77

BEV-SB: Bleeding ectopic varices in the small bowel; EIS: Enteroscopic injection sclerotherapy; IR: Interventional radiology; RBC: Red blood cells; P: Plasma.

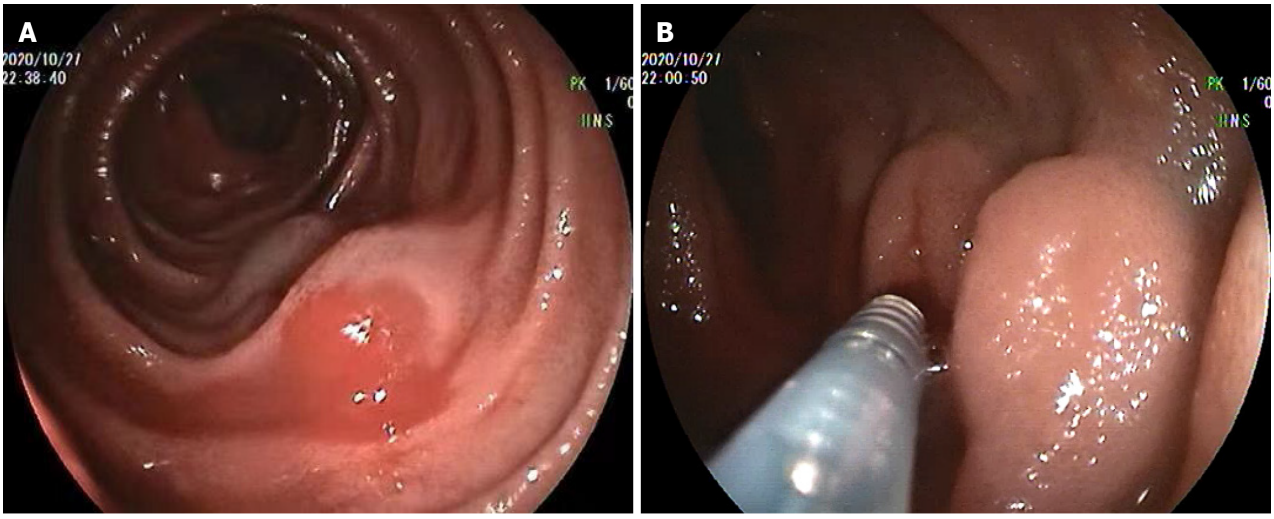

Figure 1 After verifying the bleeding ectopic varices in the small bowel, temporary hemostasis was achieved in all patients. A: Bleeding ectopic varices in the small bowel presented as elevated submucosal tortuous vessels with oozing; B: Enteroscopic injection sclerotherapy was performed with lauromacrogol injection.

In some emergencies, enteroscopic treatment may be the first choice in BEV-SB with active bleeding because of its relatively high immediate hemostasis rate and ease of performance. However, in patients who have been assessed as inaccessible for enteroscopy or in situations where enteroscopic treatment is not available, IR may be considered. In our experience, most patients can achieve temporary hemostasis with pharmacotherapy alone, making IR a selective procedure rather than an emergency. Based on the limited experience, we propose an algorithm for the treatment of BEV-SB secondary to PH (Figure 3).

In our retrospective study, we did not notice any overt hepatic encephalopathy requiring medical intervention, although it is the major potential complication of TIPS affecting almost one-third of patients. This difference may be due to a small sample bias. Furthermore, our solid follow-up strategy and post-TIPS education may also benefit to prevent hepatic encephalopathy. There was a case with post-TIPS urgent rebleeding associated with acute thrombosis of the shunt, which is an uncommon complication with a rate of fewer than 5%. Immediate restoration of patency of the stent-shunt is the pertinent management, and polytetrafluoroethylene-covered stent may help prevent this complication[15]. Since then, no overt gastrointestinal rebleeding has been observed in any of the patients in 1-3 years' follow-up, and this may be attributed to our appropriate PPG maintenance with periodic TIPS revision. Moreover, for the prehepatic PH, we achieved the "anatomical" decompression by recanalization with splenic vein stent implantation, which proved highly effective with the follow-up.

The limitations of the study, including the small sample size and single-center design, emphasize the need for larger, multi-center studies to confirm the effectiveness of the management strategies discussed in this study. Additionally, we do not consider surgical treatment as an alternative management in our center, for we have no experience in surgical treatment of BEV-SB. However, surgical treatments such as liver transplantation, surgical shunt, or splenectomy and devascularization procedures have been successfully performed in carefully selected patients, and have achieved hemostasis and blood flow reconstruction in rare situations when enteroscopic treatment and IR measures have failed

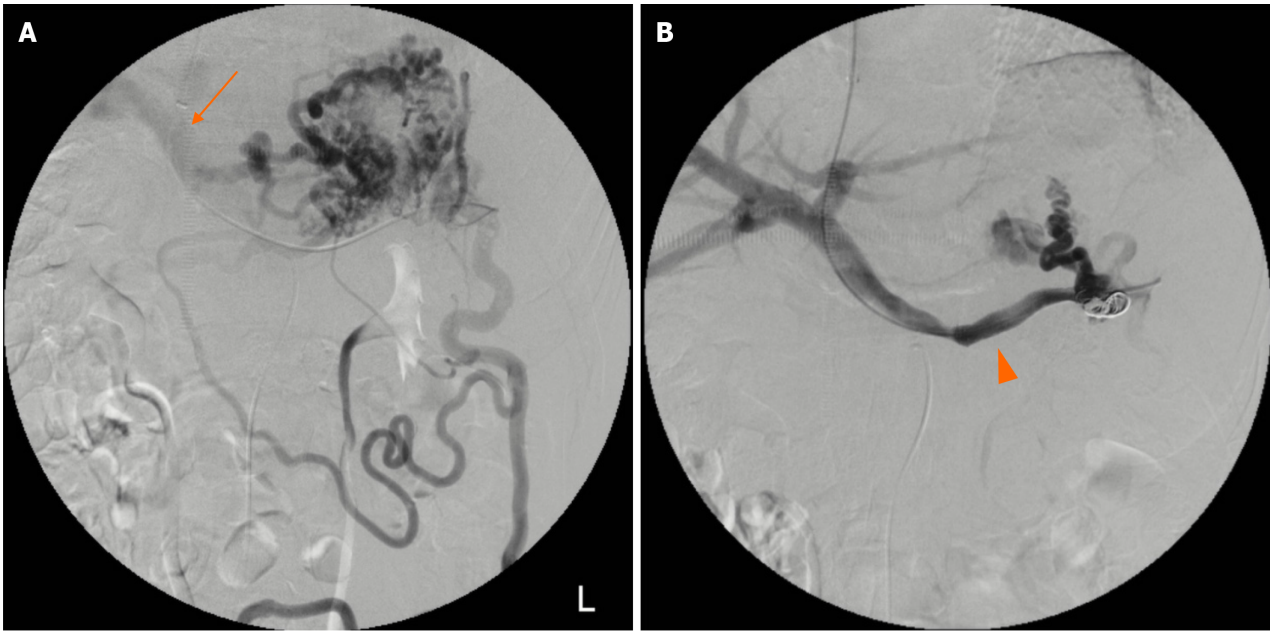

Figure 2 Recanalization was achieved by the implantation of metal stents into the splenic vein stenosis. A: Implanting a metal stent into the stenosis of the splenic vein (orange arrow); B: Recanalization was achieved (orange triangle).

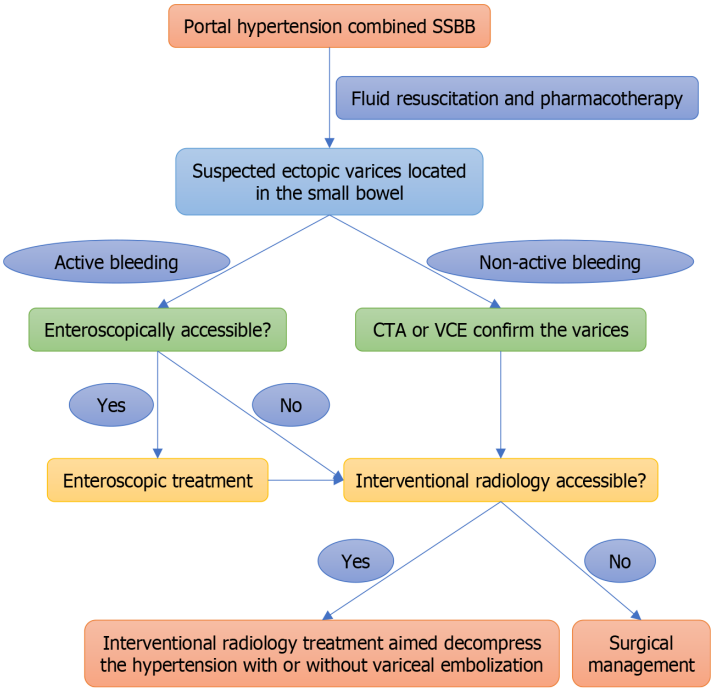

Figure 3 Management approach for patients with bleeding ectopic varices in the small bowel secondary to portal hypertension. SSBB: Suspected small bowel bleeding; CTA: Computed tomography angiography; VCE: Video capsule endoscopy.

[16]. Although surgical treatment can be effective in controlling variceal bleeding, it is highly invasive, and surgery for PH should be performed by experienced surgeons because of its complex and variable operative requirements. Compared with the minimally invasive treatment of enteroscopy or IR, surgical treatment should not be considered as a first choice unless enteroscopy and radiological management have either failed or are technically not feasible[6]. Given the complexity of BEV-SB caused by PH and the multiple treatment options available, decision-making should be based on multidisciplinary discussions between hepatologists, endoscopists, surgeons, and interventional radiologists, and an individualized treatment strategy based on local expertise and disease characteristics is important and necessary. In the future, the treatment of BEV-SB caused by cirrhotic PH or non-cirrhotic PH should be studied separately, and the treatment algorithm for these two diseases may be different.

CONCLUSION

In conclusion, EIS may serve as a bleeding control option in the initial treatment of BEV-SB. IR such as TIPS aimed at reducing PPG or recanalization of portal venous collaterals may be beneficial in reducing the rebleeding rate.

FOOTNOTES

Author contributions: Xiao NJ contributed to manuscript writing; Xiao NJ and Han ZY contributed to manuscript revision and data collection; Xiao NJ, Chu JG, Wei BJ, and Xia ZB contributed to the interventional radiology; Xiao NJ and Ning SB contributed to the enteroscopic injection sclerotherapy; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Initial experience with ultrafine choledochoscopy combined with low-dose atropine for the treatment of Oddi intersphincter stones

Xiao-Si Hu, Yong Wang, Hong-Tao Pan, Chao Zhu, Shuai Zhou, Shi-Lei Chen, Hui-Chun Liu, Qing Pang, Hao Jin

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Abstract

BACKGROUND

In recent years, the use of ultrafine choledochoscopy has gradually increased in the treatment of cholelithiasis. However, stone incarceration and residual spasm of the sphincter of Oddi may be inevitable when an ultrafine choledochoscope is used alone.

AIM

To investigate the safety and feasibility of ultrafine choledochoscopy combined with low-dose atropine in the treatment of Oddi intersphincter stones.

METHODS

Seventeen patients with Oddi intersphincter stones were retrospectively analyzed. The perioperative clinical data and follow-up information were collected.

RESULTS

Among the 17 patients, 3 were male and 14 were female. The mean age was 40.6 ± 13.9 years, and the mean diameter of the common bile duct was 7.8 ± 1.3 mm. All patients successfully underwent Oddi intersphincter stone removal using a combination of ultrafine choledochoscopy and low-dose atropine. No serious complications, such as postoperative hemorrhage, pancreatitis or bile leakage occurred in the 17 patients. During the one-year follow-up, none of the patients experienced stone recurrence.

CONCLUSION

Ultrafine choledochoscopy combined with low-dose atropine is safe and feasible for the treatment of Oddi intersphincter stones.

Key Words: Ultrafine choledochoscope; Atropine; Oddi intersphincter stone; Choledocholithiasis

Core Tip: The application of ultrafine choledochoscopy has gradually been used in the treatment of cholelithiasis. However, stone incarceration with residual stones and spasm of the sphincter of Oddi may still occur. We investigated the safety and feasibility of an ultrafine choledochoscope combined with low-dose atropine for the treatment of Oddi intersphincter stones. All 17 patients successfully underwent Oddi intersphincter stone removal using a combination of ultrafine choledochoscopy and low-dose atropine. No serious complications, such as postoperative hemorrhage, pancreatitis or bile leakage occurred. None of the patients experienced stone recurrence during follow-up. Therefore, ultrafine choledochoscopy combined with low-dose atropine is safe and feasible for the treatment of Oddi intersphincter stones.

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INTRODUCTION

Choledocholithiasis is a common disease of the biliary system that can cause serious complications such as biliary obstruction, cholangitis and pancreatitis[1,2]. Oddi intersphincter stones represent a special type of choledocholithiasis that is located in the sphincter of Oddi at the terminal common bile duct. Owing to the special anatomical site, it is relatively difficult to remove Oddi intersphincter stones. Traditional treatment methods include endoscopic retrograde cholangiopanchography combined with sphincterotomy and mechanical basket lithotomy under choledoscopy[3,4]. However, the above strategies may result in several problems, such as substantial surgical trauma, high rates of complications and incomplete stone removal[5,6].

In recent years, with the rapid progression of minimally invasive technology, the application of ultrafine choledochoscopy has gradually increased in the treatment of cholelithiasis[7]. Owing to its advantages of small diameter, flexible operation and clear field of view, the ultrafine choledochoscope can more precisely enter the Oddi intersphincter region and therefore accurately detect and remove stones. However, when used alone, the ultrafine choledochoscope may lead to stone incarceration, residual stones, and spasm of the sphincter of Oddi, which may result in surgical failure or postoperative complications.

Atropine, an anticholinergic drug, can relax smooth muscle, relieve spasm, and is widely used to treat gastrointestinal spasm. It has also been shown that atropine can relax the sphincter of Oddi[8], facilitating stone removal and improving the success rate of the operation. On the basis of the above theories and techniques, in recent years, we have innovatively applied the combination of an ultrafine choledochoscope and low-dose atropine in the treatment of Oddi intersphincter stones. In this study, we retrospectively analyzed the clinical data of 9 patients who were treated with combination therapy and explored its effectiveness and safety. This information may provide new ideas and methods for clinical treatment.

MATERIALS AND METHODS

Patients

Clinical data and surgical videos of patients with Oddi intersphincter stones admitted to the Department of Hepatopancreatobiliary, Anhui No. 2 Provincial People's Hospital from April 2021 to July 2024 were retrospectively analyzed. The inclusion criteria were as follows: (1) Aged between 18 and 75 years; (2) Terminal common bile duct stones were diagnosed using preoperative imaging, such as magnetic resonance cholangiopancreatography (Figure 1), computed tomography, and ultrasound, and Oddi intersphincter stones were further confirmed with intraoperative exploration; and (3) No obvious clinical symptoms, such as jaundice or cholangitis, were detected. The exclusion criteria were as follows: (1) Patients had serious cardiopulmonary disease, hepatic insufficiency, or renal insufficiency; (2) Patients were allergic to or contraindicated atropine; (3) Patients were pregnant or lactating; (4) Patients had uncontrolled biliary tract infection before the operation; and (5) Patients were lost to follow-up or lacked complete clinical data. Our study was reported in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Anhui No. 2 Provincial People's Hospital. All patients signed informed consent before surgery.

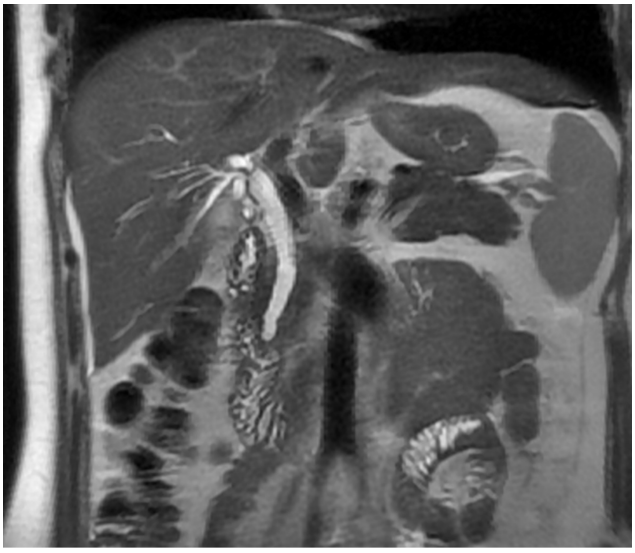

Figure 1 Magnetic resonance cholangiopancreatography showed that the stone was located in the sphincter of Oddi at the terminal common bile duct.

Equipment and materials

The ultrafine choledochoscope and related equipment were provided by Micro-Tech Co., Ltd. (host model: BS-W-150; disposable ultrafine choledochoscope model: CDS22004, diameter: 2.8 mm; disposable endoscopic lithotomy basket model: CEB01013, shape: Four-wire spiral). The amount of atropine sulfate used for injection was 0.5 mg per tablet.

Surgical procedures

Preoperative routine examinations, including routine blood tests, liver and kidney function tests, coagulation function tests and electrocardiograms, were performed. The patients were deprived of food for 4 hours and water for 2 hours before surgery. Antibiotics were administered 30 minutes before surgery to prevent infection.

General anesthesia was used, and breathing was maintained by intubation. The patients were subsequently placed in the supine position. Retrograde cholecystectomy was first performed, and the gallbladder duct was not severed. The anterior wall of the gallbladder duct was incised longitudinally at a distance of 0.5 mm from the common bile duct, and the ultrafine choledochoscope was inserted through the gallbladder duct to explore the common bile duct (Figure 2A and B). Then, under direct visual inspection using an ultrafine choledochoscope, the common bile duct was carefully examined to detect and locate Oddi intersphincter stones (Figure 2C and D). The stone was subsequently removed using a special lithotomy basket for an ultrafast choledochoscope or by being pushed into the intestinal cavity of the duodenum (Figure 2E). The common bile duct was explored once again to confirm that the stone was removed thoroughly (Figure 2F). Finally, the opening of the gallbladder duct was closed.

Before stone removal, 0.5 mg of atropine was administered intravenously, and relaxation of the Oddi sphincter was observed. If necessary, the dose was increased by 0.5 mg, and the maximum dose was 1.0 mg.

Postoperative management

The vital signs of patients were routinely observed after the operation, with special attention given to changes in breathing and heart rate. The patients were deprived of food and water for 6 hours after the operation and then gradually resumed a normal diet. Antibiotics were used continually to prevent infection. Low-dose dexamethasone (5 mg) and 654-2 (10 mg) were used in combination for 3 days. Routine blood, liver function and imaging results were reexamined at 3 days postsurgery.

Outcome indicators

The criteria for surgical success were defined as complete removal of Oddi intersphincter stone, an unblocked biliary tract, and no serious complications. The operation time was defined as the total time from the insertion of an ultrafine choledochoscope into the common bile duct to the confirmation of stone removal. Postoperative bleeding, cholangitis, pancreatitis, bile leakage, and other complications were recorded within 30 days. Patients were followed up by outpatient and telephone visits at 1, 3, 6 and 12 months after surgery. Symptom remission, stone recurrence and complications were recorded.

Statistical analysis

The Shapiro-Wilk test for normality was performed on all the data using SPSS 26.0 software. The normally distributed data are expressed as the mean ± SD. The nonnormally distributed data are expressed as the median (minimum-maximum). The categorical data are expressed as the number of cases.

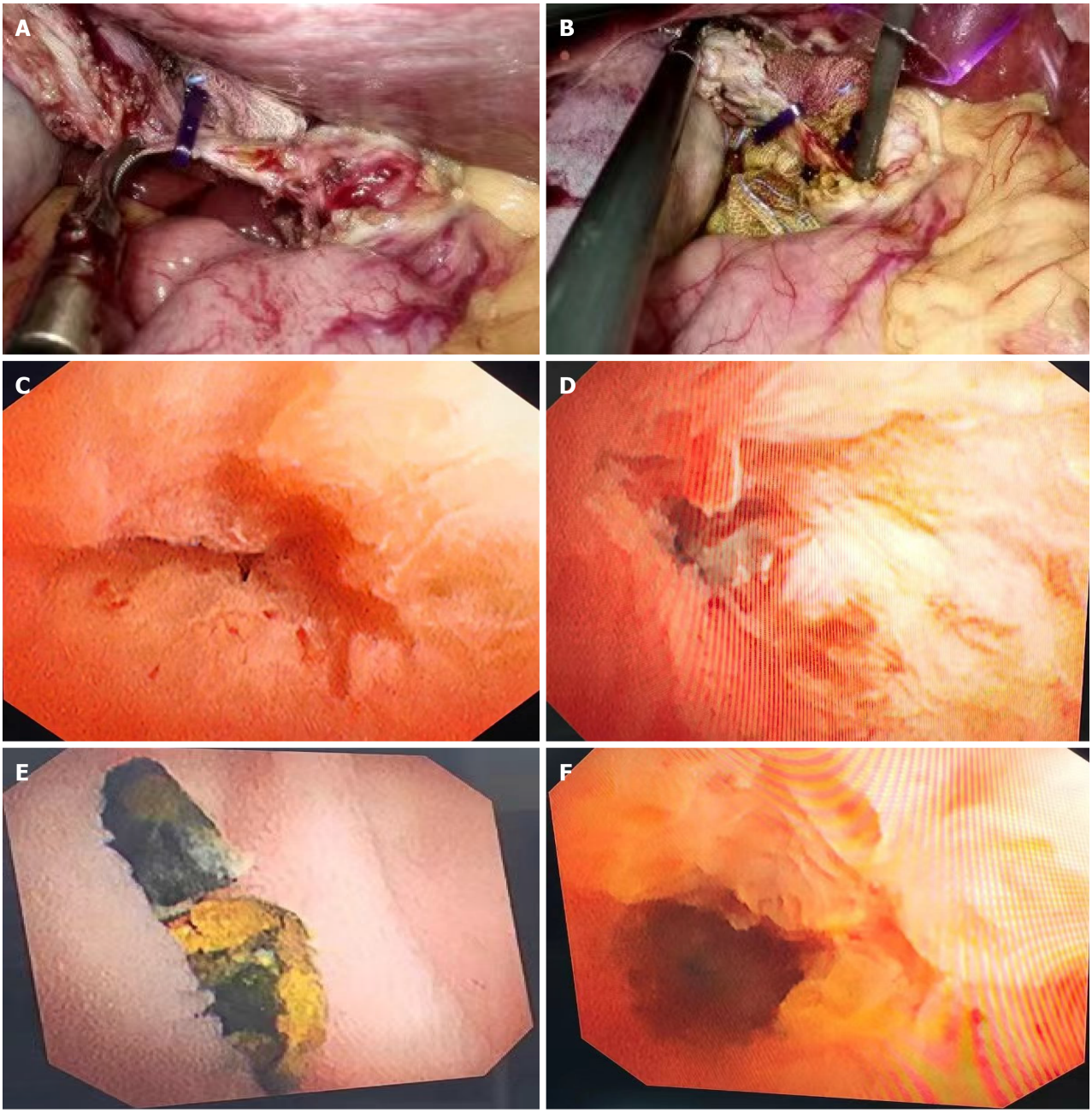

Figure 2 The process of Oddi intersphincter stone removal by ultrafine choledochoscopy combined with low-dose atropine through the gallbladder duct. A: After retrograde cholecystectomy, the anterior wall of the gallbladder duct was cut longitudinal at 0.5 mm from the common bile duct; B: Ultrafine choledochoscopy was inserted through the gallbladder duct to explore the common bile duct; C: Routine exploration of common bile duct to the terminal sphincter of Oddi showed no residual stone; D: The ultrafine choledochoscopy entered into the sphincter of Oddi, and the stones were embedded in the lower zone; E: By using atropine, the stones were pushed into the intestinal cavity; F: The surgical field of relaxation of Oddi sphincter after stone removal.

RESULTS

Basic patient information

A total of 17 patients were recruited, including 3 males and 14 females. The mean age of the patients was 40.6 ± 13.9 years, and the mean BMI was 22.1 ± 2.8 kg/m^2. The mean diameters of the common bile duct and gallbladder duct were 7.8 ± 1.3 mm and 3.8 ± 0.4 mm, respectively. The median maximum diameter of choledocholithiasis was 3 (2–5) mm, and 2 patients had multiple bile duct stones. The median preoperative TBIL level was 18 (8–51) μmol/L, and 10 patients had elevated TBIL levels. All the patients had varying degrees of symptoms, such as biliary colic, jaundice and fever. The basic information of the included patients is shown in Table 1.

Operation success rate

The stones were removed successfully in all 17 patients, with a surgical success rate of 100%. Among these patients, 12 were successfully removed through the lithotomy basket using a combination of ultrafine choledochoscopy and low-dose

Table 1 Basic information of patients, mean ± SD/median (minimum-maximum)

Variables	Total
Gender (male/female)	3/14
Age (yeas)	40.6 ± 13.9
BMI (kg/m^2)	22.1 ± 2.8
Hypertension (yes/no)	4/13
Diabetes (yes/no)	5/12
Common bile duct diameter (mm)	7.8 ± 1.3
Gallbladder duct diameter (mm)	3.8 ± 0.4
Maximum diameter of choledocholithiasis (mm)	5 (1-7)
Number of bile duct stones (single/multiple)	12/5
ALT (U/L)	61 (10-447)
AST (U/L)	49 (13-800)
ALP (U/L)	76 (42-339)
GGT (U/L)	246 (9-627)
TBIL (μmol/L)	18 (8-51)

BMI: Body mass index; ALT: Alanine aminotransferase; AST: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; TBIL: Total bilirubin.

atropine. In 5 patients, as the lithotomy basket failed to open, the stones were pushed into the intestinal cavity using a combination of ultrafine choledochoscopy and low-dose atropine.

Intraoperative conditions

The average operation time was 19.4 ± 7.8 minutes. Overall, the operation time was short, and the operation was simple. Intraoperative blood loss was 26.3 ± 7.4 mL. The postoperative durations of activity, diet, and extubation were 6.7 ± 2.0, 9.0 ± 3.4, and 1.9 ± 0.6 hours, respectively. None of the patients had postoperative jaundice (Table 2).

Postoperative complications

No serious complications, including postoperative hemorrhage, pancreatitis, bile leakage, biliary tract infection, biliary stricture, or residual stone, occurred in any of the 17 patients.

Follow-up outcomes

All patients were followed up regularly after surgery. During the follow-up period, none of the patients had preoperative symptoms such as biliary colic, jaundice or fever. The symptom remission rate was 100%. During the follow-up period, none of the patients experienced stone recurrence. No patients developed other surgery-related complications during the follow-up period.

DISCUSSION

In this study, we first demonstrated that the treatment of Oddi intersphincter stones using ultrafine choledochoscopy combined with low-dose atropine had a high success rate, a short operation time and a low incidence of postoperative complications. In addition, patient symptoms were significantly relieved, and the risk of stone recurrence was low after surgery.

An intersphincter stone is a special type of choledocholithiasis. Under traditional choledochoscopy, intermittent water injection into the common bile duct is typically applied to increase biliary pressure. The diastolic space of the Oddi sphincter was opened, and a mesh basket was used to remove the stone. Traditional choledochoscopy has an effect on upper sphincter intermuscular stones. However, owing to disturbances, the sphincter of Oddi is prone to spasms, which affect the stone removal success rate. In addition, as a traditional choledochoscope is too thick to enter the sphincter, stones located between the middle and lower sphincter are likely overlooked; therefore, the success rate of stone removal is relatively low. In addition, blindly pushing stones with mesh baskets easily causes complications such as aggravation of stone incarceration or intestinal injury. Owing to the advantages of a small diameter, flexible operation and clear vision, the ultrafast choledochoscope can better enter the Oddi intersphincter area and accurately detect and remove stones. The sphincter of Oddi is relaxed by atropine, allowing the ultrafine choledochoscope to be further extended into

Table 2 Intraoperative and postoperative data of patients, mean ± SD/median (minimum-maximum)

Variables	Total
Operation time (minute)	19.4 ± 7.8
Intraoperative blood loss (mL)	26.3 ± 7.4
Postoperative activity time (hour)	6.7 ± 2.0
Postoperative feeding time (hour)	9.0 ± 3.4
Postoperative extubation time (hour)	1.9 ± 0.6
Postoperative ALT (U/L)	56 (12-137)
Postoperative AST (U/L)	24 (12-46)
Postoperative ALP (U/L)	88 (38-218)
Postoperative GGT (U/L)	56 (7-432)
Postoperative TBIL (μmol/L)	19 (7-34)
Elevated serum amylase (yes/no)	0/17
Bile leakage (yes/no)	0/17
Biliary tract infection (yes/no)	0/17
Biliary stricture (yes/no)	0/17
Residual stone (yes/no)	0/17
Postoperative occult blood in stool (yes/no)	0/17
Stone recurrence (yes/no)	0/17
Postoperative symptom relief (yes/no)	17/0

ALT: Alanine aminotransferase; AST: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; TBIL: Total bilirubin.

the intestinal lumen, which further increases the success rate of stone removal.

In this study, Oddi intersphincter stones were successfully removed in all 17 patients by using an ultrafine choledochoscope combined with low-dose atropine, yielding a success rate of 100%. This result is consistent with a recent finding by Nie *et al*[9] that ultrafine choledochoscopy has a high success rate in the treatment of biliary stones. The complication rate of choledochoscopic surgery is approximately 7%-10%[10]. Traditional ERCP combined with sphincterotomy or mechanical lithotomy also has several shortcomings in the treatment of Oddi intersphincter stones, including large surgical trauma, high complication rates and incomplete stone removal[11]. As an anticholinergic drug, atropine relaxes smooth muscles and relieves spasms. During biliary surgery, atropine relaxes the sphincter of Oddi and improves the patency of the biliary tract, facilitating stone removal. Moreover, atropine reduces spasm reactions in the Oddi sphincter during surgery, facilitates the extraction of stones, reduces intraoperative difficulties, improves the success rate of surgery, and reduces the risk of postoperative complications[12,13]. Moreover, the dosage of atropine is controlled within a small range (0.5–1 mg), which effectively prevents adverse effects. For patients with more severe incarcerated stones, the use of intraoperative lithotripsy devices improves the removal success rate. In this study, no serious complications, such as postoperative hemorrhage, pancreatitis or bile leakage, were noted in any of the patients after surgery, suggesting that ultrafine choledochoscopy combined with low-dose atropine is safe for the treatment of Oddi intersphincter stones. As all the stones are completely removed under direct vision, the accuracy and safety of treatment could be significantly improved[14]. Therefore, ultrafine choledochoscopy through the gallbladder duct combined with low-dose atropine has the advantages of less trauma, faster postoperative recovery, and fewer complications. For patients with a history of cholecystectomy, an ultrafine choledochoscope could be inserted through the gallbladder duct, and this technique could also be used as a new treatment for Oddi intersphincter stones.

Although the present study results indicate that ultrafine choledochoscopy combined with low-dose atropine has a satisfactory effect on the treatment of Oddi intersphincter stones, the sample size of the study was relatively small, and a control group was lacking. It is necessary to increase the sample size and establish a control group to further verify the effectiveness and safety of this technology. In addition, the optimal dosage and timing of atropine should be further explored to optimize the treatment regimen.

CONCLUSION

In conclusion, this study suggests that ultrafine choledochoscopy combined with low-dose atropine is effective and safe for the treatment of Oddi intersphincter stones, with a high surgical success rate, a low incidence of postoperative

complications, and a low risk of stone recurrence. This method provides new ideas and choices for the minimally invasive treatment of biliary calculi and has good clinical application prospects.

FOOTNOTES

Author contributions: Hu XS and Wang Y prepared this manuscript; Pan HT and Zhou S performed the statistical analysis and the literature research; Hu XS, Zhu C and Chen SL contributed to data collection and analysis; Jin H and Pang Q played indispensable roles in the study design, data analysis and manuscript preparation as the co-corresponding authors; Jin H conceptualized, designed, and supervised the whole process of the study; Pang Q was responsible for data re-analysis, figures and tables plotting, language polishing, and literature search. This collaboration between Jin H and Pang Q is crucial for the publication of this manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Therapeutic effectiveness and influencing factors of laparoscopic appendectomy with mesoappendix dissection in the treatment of acute appendicitis

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Abstract

BACKGROUND

Acute appendicitis (AP) is a frequently encountered surgical emergency, and appendectomy is conventionally regarded as the predominant treatment modality. Nevertheless, the therapeutic efficacy of this surgical approach remains to be improved. Thus, the exploration and implementation of surgical refinements are necessary.

AIM

To elucidate the therapeutic effectiveness and influencing factors of laparoscopic appendectomy (LA) with mesoappendix dissection in the treatment of AP.

METHODS

First, 150 patients with AP who visited Shangrao Municipal Hospital between January 2022 and June 2024 were enrolled in this study. Among them, 72 patients were assigned to the control group to receive conventional LA, whereas 78 cases were included in the observation group for LA with mesoappendix dissection. Subsequently, indicators such as therapeutic effectiveness, surgical indices (operation time, intraoperative blood loss, and hospital stay), postoperative recovery indices (time to ambulation, gastrointestinal function recovery time, and time to food intake), incidence of adverse events (postoperative bleeding, pelvic infection, puncture site infection, and ileus), and serum inflammatory factors [tumor necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein (CRP)] were collected and comparatively analyzed, and the influencing factors of therapeutic effectiveness in patients with AP were analyzed.

RESULTS

Compared with the control group, the observation group had higher clinical therapeutic effectiveness, less operation time, intraoperative blood loss, and hospital

stay; shorter time to ambulation, gastrointestinal function recovery, and food intake; and a lower total incidence of adverse events, and this difference is statistically significant. In addition, the expression levels of various serum inflammatory factors in the observation group were significantly reduced postoperatively, which were markedly lower than those in the control group. Moreover, sex, age, body mass index, time from acute onset to admission, family medical history, preoperative TNF-α, preoperative IL-6, preoperative CRP, and treatment modality were identified to be not independent factors affecting the therapeutic effectiveness of LA with mesoappendix dissection in patients with AP.

CONCLUSION
Overall, LA with mesoappendix dissection has a remarkable curative effect in treating patients with AP, which is worthy of clinical promotion.

Key Words: Laparoscopy; Appendectomy with mesoappendix dissection; Acute appendicitis; Therapeutic effectiveness; Analysis of influencing factors

Core Tip: At present, relevant research focusing on the efficacy and influencing factors of laparoscopic appendectomy with mesoappendix dissection in treating patients with acute appendicitis is limited. In this study, 150 patients who are suffering from acute appendicitis were enrolled. Comparative analyses regarding the clinical application of conventional laparoscopic appendectomy and laparoscopic appendectomy with mesoappendix dissection were performed among these patients, taking into account therapeutic effectiveness, surgical parameters, postoperative rehabilitation, the occurrence rate of adverse events, and serum inflammatory factors. Finally, we concluded that laparoscopic appendectomy with mesoappendix dissection, when applied to treat patients with acute appendicitis, can enhance the treatment efficacy and surgical outcomes, facilitating patients' postoperative recovery, decreasing the incidence of adverse events, and averting the excessive increase of inflammatory markers, including tumor necrosis factor-α, interleukin-6, and C-reactive protein triggered by surgical stimuli. Hence, this approach shows great potential in clinical application.

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INTRODUCTION

Acute appendicitis (AP) is a common surgical emergency with a lifetime morbidity risk in the range of 6%-7%, with 300000 appendectomies performed annually in the United States alone[1,2]. Statistically, AP has a higher incidence in males, with a morbidity risk of 8.6%, than in females (6.7%)[3]. This disease is primarily induced by fecaliths, fecal impaction, lymphoid hyperplasia, or tumors, which can trigger edema, vascular congestion, ischemia, appendiceal perforation, and intra-abdominal abscess or generalized peritonitis[4]. The main clinical manifestations of AP include nausea, vomiting, anorexia, abdominal pain, and fever, which have diverse degrees of negative impacts on the physical health of patients[5]. Appendectomy is the first treatment option for AP. Given the development and widespread application of laparoscopic technology, laparoscopic appendectomy (LA) has advantages such as small wounds, aesthetically pleasing incisions, and rapid postoperative recovery in clinical practice[6,7]. LA involves extracting the patient's appendix through the trocar puncture hole. However, for patients with severe swelling, LA is challenging[8,9]. Moreover, if the patient has relatively severe mesenteric edema and adhesion, then LA is often accompanied with mesenteric torsion, thereby increasing the difficulty of the operation and the risk of mesenteric bleeding at the root of the appendix [10-12]. Thus, this study aims to improve the surgical outcome of patients with AP by LA combined with mesoappendix dissection. LA with mesoappendix dissection is an improved surgical modality of conventional LA, which reduces the size of the specimen by removing the appendix root and mesoappendix, making the specimen easy to remove and reducing the risk of active bleeding[13,14]. Given the current dearth of research on the therapeutic effectiveness and influencing factors of LA with mesoappendix dissection for the treatment of AP, this study aims to conduct relevant analysis to improve surgical outcomes in such patients.

MATERIALS AND METHODS

Collection of patient information

Patients were included in the study if they met the following criteria: Patients were diagnosed of AP by computerized tomography, surgical physical examination, abdominal B-ultrasound, and blood routine examination in combination with physical examination and medical history[15]; patients with acute onset; patients presented with typical clinical symptoms such as vomiting and right lower abdominal pain; patients completed the surgical indications for appendectomy; patients have complete clinical data. The exclusion criteria were as follows: Perforated appendix; inability to tolerate general anesthesia; history of laparoscopic surgery and conversion to open surgery during the operation; impaired cardiac, pulmonary, and renal functions; severe complications such as appendiceal abscess and perforation; suppurative portal phlebitis, peritonitis, and internal and external fistulas; onset time > 3 days. This research was approved by the Shangrao Municipal Hospital Ethics Committee without reserves. After rigorous screening in accordance with the abovementioned inclusion and exclusion criteria, 150 patients with AP who were admitted to Shangrao Municipal Hospital from January 2022 to June 2024 were selected as the research subjects. These patients were divided into two groups, 72 in the control group who received conventional LA and 78 in the observation group who were treated by LA with mesoappendix dissection.

Surgical procedures

Both groups of patients maintained a supine position during the surgery. A three-port approach was used. First, a 10 mm trocar was placed 1 cm above the upper edge of the umbilicus, which served as the intraoperative observation port and connected to the pneumoperitoneum tube. Carbon dioxide pneumoperitoneum was routinely established with a pressure range of 11-12 mmHg. Then, a 10 mm trocar was inserted 2 cm below and parallel to the umbilicus on the midline of the patient's left clavicle, which served as the main intraoperative operating port. A 5 mm trocar was placed at the left counter-McBurney's point, which served as the intraoperative traction port.

The control group was treated with conventional LA. A puncture was created between the serosal surface of the appendix and the mesoappendix at the root of the patient's appendix by using a surgical ultrasonic scalpel, and the distal end of the appendix and mesoappendix was clamped. Subsequently, the appendix and mesoappendix were sequentially severed and removed *via* the main operation port. Thereafter, the puncture site was disinfected with iodophor solution and routinely sutured. Both groups were treated under intraoperative conditions to determine whether an indwelling drain was placed.

For the observation group, LA combined with mesoappendix dissection was performed. A surgical ultrasonic scalpel was used to cut the mesoappendix to the serosal surface of the appendix from the end to the apex of the patient's appendix. Then, the mesoappendix was peeled off along the serosal surface of the appendix toward the end of the appendix until the root of the appendix. Next, the appendix and distal end of the mesoappendix root were clamped. The appendix and mesoappendix were sequentially severed using the surgical ultrasonic scalpel and then removed from the main operation port (trocar). Finally, the interior of the puncture site was disinfected with iodophor solution and routinely sutured.

Evaluation indexes

Therapeutic effectiveness: The clinical effectiveness of the two groups was comparatively analyzed in accordance with the following criteria for efficacy determination: The complete disappearance of symptoms and signs is considered markedly effective; the partial alleviation of symptoms and signs is regarded as effective; the absence of change or aggravation of symptoms and signs is deemed ineffective. The total effective rate of treatment was measured as the sum of the number of markedly effective cases and effective cases as a percentage of the total number of cases.

Surgical indices: Operation time, intraoperative blood loss, and hospital stays were observed and recorded.

Postoperative recovery indices: The time to ambulation, gastrointestinal function recovery, and food intake of both groups of patients were observed and recorded.

Incidence rate of adverse events: The incidence of adverse reactions such as postoperative bleeding, pelvic infection, puncture site infection, and ileus was observed and recorded.

Serum inflammatory factors: Five milliliters of fasting venous blood was collected from patients before and after treatment, and the serum was centrifuged to determine the level of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein (CRP) levels by enzyme-linked immunosorbent assays.

Statistical analysis

Statistical analysis was conducted using SPSS 19.0, with $P < 0.05$ indicating statistical significance. Measurement data were statistically described as (mean ± SD), with inter-group and intra-group comparisons before and after treatment performed by using an independent sample *t*-test and paired *t*-test, respectively. Count data were represented as *n* (%), and a χ^2 test was performed for inter-group comparisons.

RESULTS

Patient general information

No notable differences in sex, age, body mass index (BMI), time from acute attack to admission, and family medical history were found between the control and observation groups ($P > 0.05$; Table 1).

Comparative analysis of therapeutic effectiveness

The total number of effective cases in the control and observation groups was 60 and 74, respectively, with a markedly higher total effective rate in the observation group than in the control group ($P < 0.05$; Table 2).

Surgical indices of the two groups

Compared with the control group, the operation time, intraoperative blood loss, and hospital stay in the observation group were statistically shorter ($P < 0.001$; Table 3).

Postoperative recovery indices of the two groups

The observation group had markedly shorter time to postoperative ambulation, gastrointestinal function recovery, and food intake than the control group ($P < 0.001$; Table 4).

Incidence rate of adverse events in two groups

By counting the incidence of adverse events such as postoperative bleeding, pelvic infection, puncture site infection, and ileus in the two groups, we found that the total incidence of adverse events was significantly lower in the observation group than in the control group ($P < 0.05$; Table 5).

Serum inflammatory factors between the two groups

The two groups showed the same preoperative TNF-α, IL-6, and CRP levels ($P > 0.05$). Postoperatively, these indexes evidently increased in both groups but with lower levels in the observation group than in the control group (all $P < 0.05$; Figure 1).

Analysis of factors influencing patient efficacy

Based on logistic regression analysis, sex, age, BMI, time from acute attack to admission, family medical history, preoperative TNF-α, preoperative IL-6, preoperative CRP, and treatment modality were considered to be not independent factors influencing patient efficacy ($P > 0.05$; Table 6).

DISCUSSION

The etiology of AP is intricate. Factors such as diet, genetics, ischemia, inflammation, and fecalith-induced lumen obstruction serve as risk factors for the occurrence of AP[16]. The pathological mechanism of AP entails appendiceal dilation resulting from the obstruction of the appendiceal orifice, thereby influencing the normal drainage of its contents. The stagnant contents and increased bacterial load in the appendix can initiate excessive inflammation, which leads to appendiceal infection and inflammation, thereby triggering AP[17,18]. Timely and effective surgical intervention for this disease is conducive to averting serious complications such as appendiceal perforation[19]. In this study, LA with mesoappendix dissection was proposed for the treatment of AP, and this treatment modality was compared with conventional LA to validate its clinical superiority.

First, the total effective rate of treatment in the observation group of patients undergoing LA with mesoappendix dissection was remarkably high, indicating that LA with mesoappendix dissection for patients with AP can maximize the therapeutic efficacy and facilitate the amelioration of patients' symptoms and signs. In addition, the operation time, intraoperative blood loss, hospital stay, time to ambulation, gastrointestinal function recovery, and food intake in patients with AP treated by LA with mesoappendix dissection were significantly less, indicating that this therapeutic approach can improve the surgical outcomes of patients with AP and promote postoperative recovery compared with conventional LA. Moreover, LA with mesoappendix dissection can simplify intraoperative hemostasis compared with conventional LA, which is conducive to shortening the operation time[20]. Meanwhile, this therapy can separate and remove the appendix and mesoappendix, which reduces the surgical difficulty of appendectomy[21]. With regard to safety, the overall incidence of adverse events such as postoperative bleeding, pelvic infection, puncture site infection, and ileus in patients under LA with mesoappendix dissection was significantly low, indicating that this surgical procedure can reduce the risk of the abovementioned adverse events. During LA with mesoappendix dissection, a laparoscope was used to magnify the fine structure of the body and to achieve broad exploration of the abdominal cavity, which not only facilitates the determination of the appendix location and reduces the interference with the abdominal cavity, but also decreases the risk of surgery-related adverse events to a certain extent[22]. Furthermore, this surgical technique utilizes a surgical ultrasonic scalpel to transect the mesentery at the distal end of the mesoappendix and to dissect the mesentery at the serosal surface of the appendix, which can prevent active bleeding during the operation to the greatest extent and reduce the stimulation to the patient's abdominal organs[23]. Moreover, the small sample size obtained can reduce the risk of contact with intra-abdominal pus and purulent coating, thereby decreasing the incidence of adverse events[24]. The safety of LA with mesoappendix dissection, which to a certain extent prevents the occurrence of postoperative adverse events, can promote

Table 1 Patient general information

General information	Control group (*n* = 72)	Observation group (*n* = 78)	χ^2/t	*P* value
Sex (male/female)	42/30	44/34	0.057	0.812
Age (years)	48.36 ± 6.18	49.03 ± 7.56		
Body mass index (kg/m^2)	23.58 ± 2.37	24.32 ± 2.55		
Time from acute onset to admission (hour)	24.01 ± 3.16	23.64 ± 3.24		
Family medical history (without/with)	64/8	67/11	0.303	0.582

Measurement data were statistically described as (mean ± SD).

Table 2 Therapeutic effectiveness of the two groups, *n* (%)

Therapeutic effectiveness	Control group (*n* = 72)	Observation group (*n* = 78)	χ^2	*P* value
Markedly effective	25 (34.72)	35 (44.87)		
Effective	35 (48.61)	39 (50.00)		
Ineffective	12 (16.67)	4 (5.13)		
Total	60 (83.33)	74 (94.87)	5.231	0.022

Table 3 Surgical indices of the two groups

Surgical indices	Control group (*n* = 72)	Observation group (*n* = 78)	*t*	*P* value
Operation time (minute)	50.76 ± 6.42	43.96 ± 4.97	7.285	< 0.001
Intraoperative blood loss (mL)	37.00 ± 7.38	24.64 ± 6.24	11.104	< 0.001
Hospital stay (day)	7.24 ± 2.63	5.47 ± 1.73	4.905	< 0.001

Measurement data were statistically described as (mean ± SD).

Table 4 Postoperative recovery indices of the two groups

Postoperative recovery index	Control group (*n* = 72)	Observation group (*n* = 78)	*t*	*P* value
Time to ambulation (hour)	27.90 ± 4.80	22.37 ± 3.98	7.703	< 0.001
Time to gastrointestinal function recovery (day)	3.42 ± 1.32	2.15 ± 0.90	6.930	< 0.001
Time to food intake (day)	3.76 ± 1.27	2.69 ± 1.02	5.709	< 0.001

Measurement data were statistically described as (mean ± SD).

Table 5 Incidence rate of adverse events in two groups, *n* (%)

Postoperative recovery indexes	Control group (*n* = 72)	Observation group (*n* = 78)	χ^2	*P* value
Postoperative bleeding	5 (6.94)	2 (2.56)		
Pelvic infection	3 (4.17)	1 (1.28)		
Puncture site infection	3 (4.17)	0 (0.00)		
Ileus	1 (1.39)	0 (0.00)		
Total	12 (16.67)	3 (3.85)	6.838	0.009

Table 6 Multivariate analysis of factors influencing patient efficacy

Factor	β	SE	Wald	*P* value	Exp (β)	95%CI
Sex	-0.088	0.566	0.024	0.876	0.915	0.302-2.777
Age	-0.015	0.044	0.122	0.726	0.985	0.904-1.073
Body mass index (kg/m^2)	-0.109	0.116	0.883	0.347	0.897	0.714-1.126
Time from acute onset to admission (hour)	0.144	0.105	1.902	0.168	1.155	0.941-1.418
Family medical history	-0.214	0.916	0.054	0.816	0.808	0.134-4.861
Preoperative TNF-α (ng/L)	-0.872	0.941	0.859	0.354	0.418	0.066-2.643
Preoperative IL-6 (pg/mL)	-0.007	0.030	0.058	0.809	0.993	0.937-1.052
Preoperative CRP (mg/L)	0.065	0.115	0.319	0.572	1.067	0.852-1.335
Treatment modality	1.214	0.621	3.820	0.051	3.368	0.997-11.380

TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; CRP: C-reactive protein.

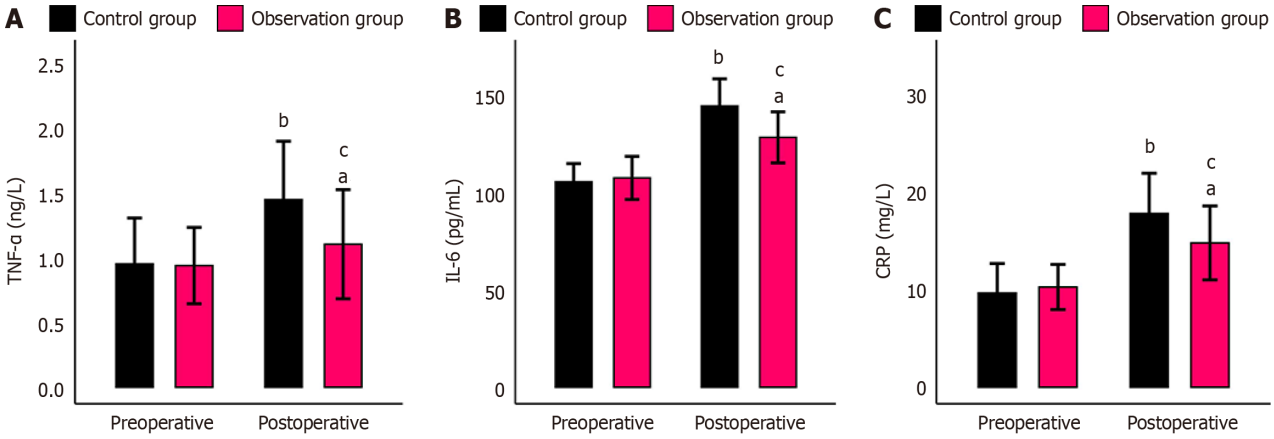

Figure 1 Serum inflammatory factors in two groups. A: Pre- and post-operative tumor necrosis factor-α levels in the two groups; B: Pre- and post-operative interleukin-6 levels in the two groups; C: Pre- and post-operative C-reactive protein levels in the two groups. $^aP < 0.05$ and $^bP < 0.01$ compared with the preoperative level within the group; $^cP < 0.05$ compared with the control group; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; CRP: C-reactive protein.

the smooth postoperative recovery of patients[25]. In addition, this surgical method can reduce postoperative abnormally elevated inflammatory markers such as TNF-α, IL-6, and CRP, indicating that LA with mesoappendix dissection can markedly suppress serum inflammation. This effect may be attributed to the small trauma to the body during the operation of this surgical therapy, which to a certain extent ameliorates inflammatory stress[26]. Finally, binary logistic regression analysis confirmed that sex, age, BMI, time from acute attack to admission, family medical history, preoperative TNF-α, preoperative IL-6, preoperative CRP, and treatment modality were not risk factors affecting patient's curative effect. Many researchers have also considered other modified approaches to appendectomy. For example, Liu *et al*[27] reported that single-incision transumbilical LA, when implemented in children with AP, has remarkable superiority with regard to pain alleviation and enhancement of cosmetic appearance compared with the conventional three-port LA. Moreover, Zhang *et al*[28] noted that the modified endoscopic retrograde appendicitis therapy can achieve a surgical success rate of 96.9% among children with uncomplicated (simple) AP, and the recurrence risk within a 1-year period is merely 6.9%.

Notwithstanding the demonstration of the clinical effectiveness, safety, and other clinical advantages of LA with mesoappendix dissection in patients with AP, this study still has several limitations that necessitate further amelioration. First, the sample recruitment for this study was confined to a single center, and the temporal scope of the investigation was hindered. The expansion of the research sample pool by incorporating data from multiple centers over a more prolonged period would incontrovertibly augment the accuracy and reliability of the research findings. Second, the allocation of surgical modalities in this study might be susceptible to biases caused by the age of patients upon admission, the duration of symptom manifestation, and the predilection of the surgeons involved. Finally, relevant investigations regarding immune-related indices are lacking. The supplementation of such analyses could provide deeper insights into the potential influence of the two surgical methods on the immune function of patients. Future research initiatives will be directed toward progressively enhancing and refining this study by addressing the aforementioned concerns.

CONCLUSION

Based on the results, LA with mesoappendix dissection for the treatment of patients with AP can enhance curative efficacy and surgical outcomes, facilitate postoperative rehabilitation, decrease the incidence of adverse events, and prevent excessive elevation of inflammatory markers such as TNF-α, IL-6, and CRP caused by surgical stimulation, indicating its great potential for clinical applications.

FOOTNOTES

Author contributions: Yuan J designed and performed the research; Yuan J and Wu BY designed the research and supervised the report; Yuan J, Liu Q and Wu BY collected and analyzed data; All authors approved the final manuscript.

Institutional review board statement: This study was approved by the Ethic Committee of Shangrao Municipal Hospital on June 21, 2024.

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ORIGINAL ARTICLE

Retrospective Study

Comparative analysis of Ferguson hemorrhoidectomy combined with doppler-guided hemorrhoidal artery ligation and Ferguson hemorrhoidectomy in hemorrhoidal disease treatment

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Abstract

BACKGROUND

In hemorrhoidal disease, despite the existence of numerous treatment options to alleviate symptoms, surgical intervention continues to be the gold standard. The advantages and disadvantages of many methods have been shown in numerous studies However, only a few studies have compared the effectiveness of combined methods.

AIM

To compare the results of a coloproctology clinic that switched to the Doppler-guided hemorrhoidal artery ligation (DG-HAL) + Ferguson hemorrhoidectomy (FH) technique from the FH in the treatment of hemorrhoidal disease.

METHODS

In this retrospective cohort, data from a total of 45 patients who underwent DG-HAL + FH (n = 24) and FH (n = 21) for grade III hemorrhoidal disease between 2020 and 2022 were analyzed. Demographic and clinical data, surgical duration, intraoperative blood loss, hospital stay, postoperative analgesic consumption, pain scores using the Visual Analog Scale (VAS), complications, time to return to normal activities, and the recurrence rate were compared in both groups.

RESULTS

The study included 45 patients, with 75.6% (n = 34) male and 24.4% (n = 11) female. The rate of intraoperative blood loss was higher in the FH group (P < 0.05). The VAS scores and postoperative complication rates were similar in both groups. The need for postoperative analgesics was lower in the DG-HAL + FH group (2 *vs* 4 days, P < 0.05), while the FH group showed a shorter time to return to normal activities (9.5 *vs* 6.0 days, P = 0.02). The recurrence rate (16.7% *vs* 0%) and Clavien–Dindo Score-1 complications (20.8% *vs* 9.5%, P = 0.29) were higher in

the DG-HAL + FH group but were insignificant.

CONCLUSION
Our study revealed that the addition of the DG-HAL to classical hemorrhoidectomy caused less intraoperative bleeding and a lower postoperative analgesia requirement.

Key Words: Hemorrhoidal disease; Doppler-guided hemorrhoidal artery ligation; Ferguson hemorrhoidectomy; Postoperative pain; Recurrence

Core Tip: In the contemporary treatment of hemorrhoidal disease, there is a broad spectrum of methods ranging from conservative treatments to stapled hemorrhoidectomy. The purpose of choosing combined therapy was to avoid undesirable complications such as pain and anal stenosis associated with conventional hemorrhoidectomies and to prevent potential tissue and sensory loss. We thought that non-invasive methods like Doppler or laser pexy might not be sufficient in some cases, while excision could be beneficial for prolapsed hemorrhoids. In this study, we compared the combined Ferguson approach [Ferguson + Doppler-guided hemorrhoidal artery ligation (DG-HAL)] with Ferguson hemorrhoidectomy only. We found that the duration of postoperative analgesic need was significantly lower in the DG-HAL + hemorrhoidectomy group, and the return to normal activity was quicker in Ferguson hemorrhoidectomy group.

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INTRODUCTION

Hemorrhoids, identifiable as "vascular cushions" in the anorectal component contributing to the physiological continence mechanism, can expand due to various reasons, leading to hemorrhoidal disease characterized by symptoms such as bleeding, pain, and itching. Hemorrhoidal disease is a common and life quality-diminishing issue in society. Due to many cases being asymptomatic, its exact prevalence is unknown. The prevalence in the adult population varies from 4% to 45%, making hemorrhoidal disease the most frequent reason for proctology consultations, and it is found in up to 70% of the working population[1,2].

In hemorrhoidal disease, despite the existence of numerous treatment options to alleviate symptoms, surgical intervention continues to be the gold standard, particularly for grade 3-4 hemorrhoidal disease which is resistant to conservative treatment, according to the Goligher classification. Open hemorrhoidectomy (Milligan–Morgan) or closed hemorrhoidectomy (Ferguson) is one of the most commonly utilized operations[3-5]. However, this operation is associated with various complications, such as postoperative pain, bleeding, and anal stenosis, leading to patients' apprehension toward the surgical procedure. This situation has prompted the development of additional surgical procedures. In recent years, surgeons have shifted the treatment paradigm toward less-invasive techniques such as sclerotherapy, laser, hemorrhoidal artery ligation, and rubber band ligation with the aim to minimize the pain and complications resulting from the anatomical excisions of hemorrhoids[6-10].

Theoretically, Doppler-guided hemorrhoidal artery ligation (DG-HAL) is a procedure where hemorrhoidal arteries are ligated using a device aided by a Doppler-equipped anoscope. Through adding mucopexy, this technique aims to prevent prolapse of the hemorrhoidal and mucosal tissue. This technique is also called DG-HAL + recto anal repair. It has been proposed as an effective and painless technique for treating symptomatic grade 2 and 3 hemorrhoids with minimal mucosal prolapse[11].

Debates continue regarding the selection of a treatment for hemorrhoidal disease. The advantages and disadvantages of many methods have been shown in numerous studies[12-15]. However, only a few studies have compared the effectiveness of combined methods[3,5,16]. There is a lack of studies in the literature comparing the efficacy and outcomes of combined DG-HAL+ Ferguson hemorrhoidectomy (FH) *vs* FH alone.

This study compared the DG-HAL + FH *vs* the classic FH technique in treating hemorrhoidal disease.

MATERIALS AND METHODS

This study was conducted by a National and International Board-certified coloproctologist in the colorectal surgery unit of a university hospital where more than 400 colorectal surgical procedures are performed annually. The ethics committee

approval for writing the article was received from the Cukurova University Faculty of Medicine Ethics Committee in November 2023 (Approval No: 138).

The study included patients who applied to the coloproctology clinic between 01 January, 2020 and 30 December, 2022. The device/proctoscope with a Doppler converter (Angiodin-proctor by Comepa) began to be routinely used in our clinic on 15 June, 2021. Before this date (from 01 January, 2020 to 15 June, 2021), FH was performed routinely. Since the provision of the Doppler device, either DG-HAL or DG-HAL+FH have been routinely used for the treatment of grade 2 and 3 hemorrhoids.

Inclusion criteria: Patients aged between 18 and 65 years with grade 3 hemorrhoidal disease that did not respond to medical treatment or lifestyle changes were included in the study. Patients who underwent only FH or DG-HAL + FH were included in the study.

Exclusion criteria: Patients with a history of anorectal surgery or benign proctological diseases (*e.g.*, perianal fistula, rectal prolapse, anal fissure, fecal incontinence, or anal stenosis) were excluded. Patients who underwent stapled hemorrhoidopexy, laser hemorrhoidopexy, or Milligan–Morgan hemorrhoidectomy were excluded from the study. Patients with grade 1-2-4 hemorrhoidal diseases were excluded. Patients who underwent only DG-HALs (without excisional hemorrhoidectomy) for grade 2 hemorrhoidal disease were also excluded from the study.

The patients were divided into groups based on the surgical treatment received: Group 1 (DG-HAL + FH) and group 2 (FH alone).

Preoperative preparation

Preoperative colonoscopy or sigmoidoscopy was performed on patients in the colorectal screening age groups defined by the Turkish Ministry of Health and those suspected of having rectal cancer (due to age, presence of tenesmus, or a family history of colorectal cancer).

All patients received a phosphate enema approximately 3 hours before surgery. Antibiotic prophylaxis with 500 mg metronidazole was administered in the operating room.

Surgical technique

All surgical procedures were performed by the same surgeon experienced in coloproctological surgery. The surgeries were performed under standard spinal anesthesia, with the patient in the lithotomy position.

FH was performed using the standard technique described in the literature, with the excision of the hemorrhoidal tissue carried out using electrocautery and closure of the excised hemorrhoidal tissue sites using absorbable sutures.

In the combined method (DG-HAL + FH), 1 or 2 dominant and prolapsed hemorrhoid piles were excised using the Ferguson technique (Figure 1), followed by DG-HAL on 1 or 2 piles. In cases where DG-HAL was performed as part of the combined procedure, the larger pile was designated as the dominant one and excised, while ligation was applied to the other piles. A maximum of three piles were treated for each patient in all groups. For DG-HAL, a special device/proctoscope with a Doppler converter was inserted into the anal canal and distal rectum (Figure 2). After placement, each branch was tied approximately 3-4 cm above the dentate line with a 2-0 absorbable polyglycolic acid suture, and the device was rotated clockwise to locate other arteries at that level. After a full rotation, the procedure was repeated up to 0.5-1 cm below the first series of sutures. Continuous sutures, becoming more superficial towards the dentate line, were placed, starting 3 cm proximal to the dentate line and ending 0.5 cm to the dentate line in patients with prolapsed hemorrhoids and/or rectal mucosal prolapse and tied to complete the mucopexy.

Post-discharge management included dietary modifications (*e.g.*, stool softeners, adequate fluid intake with fiber supplements) and standard medical treatment. Venotonics were routinely prescribed.

Follow-up

After discharge, patients were routinely assessed on the 14th post-operative day in the outpatient clinic. Digital rectal examinations and/or rectoscopy were performed within 3-6 months to check for recurrences. Telephone interviews were conducted to assess the patients' last status one year after the surgery.

Evaluation criteria and outcome measures

Demographic data such as age and gender were compared. Key performance indicators included intraoperative blood loss, length of hospital stay, postoperative analgesic requirement, and time to return to normal daily activities. Visual analog scale (VAS) scores were prospectively recorded after every procedure. The patients scored (0 = no pain, 10 = worse pain) the average pain and the pain after defecation. Early postoperative complications were classified according to the Clavien-Dindo (CD) scale. Urinary retention and tenesmus were classified as CD-1.

Statistical analysis

Statistical analysis was conducted using the SPSS v24 (IBM) software. Numerical variables are presented with their mean and standard deviation or median, minimum, and maximum values, while categorical variables are expressed in terms of counts and percentages. For group comparisons, the χ^2 test was used to analyze categorical variables, while the Mann–Whitney *U*-test was applied for non-normally distributed continuous variables. Changes in VAS scores between days 1 and 7 within groups were evaluated using the Wilcoxon signed-rank test. A *P* value less than 0.05 was considered statistically significant.

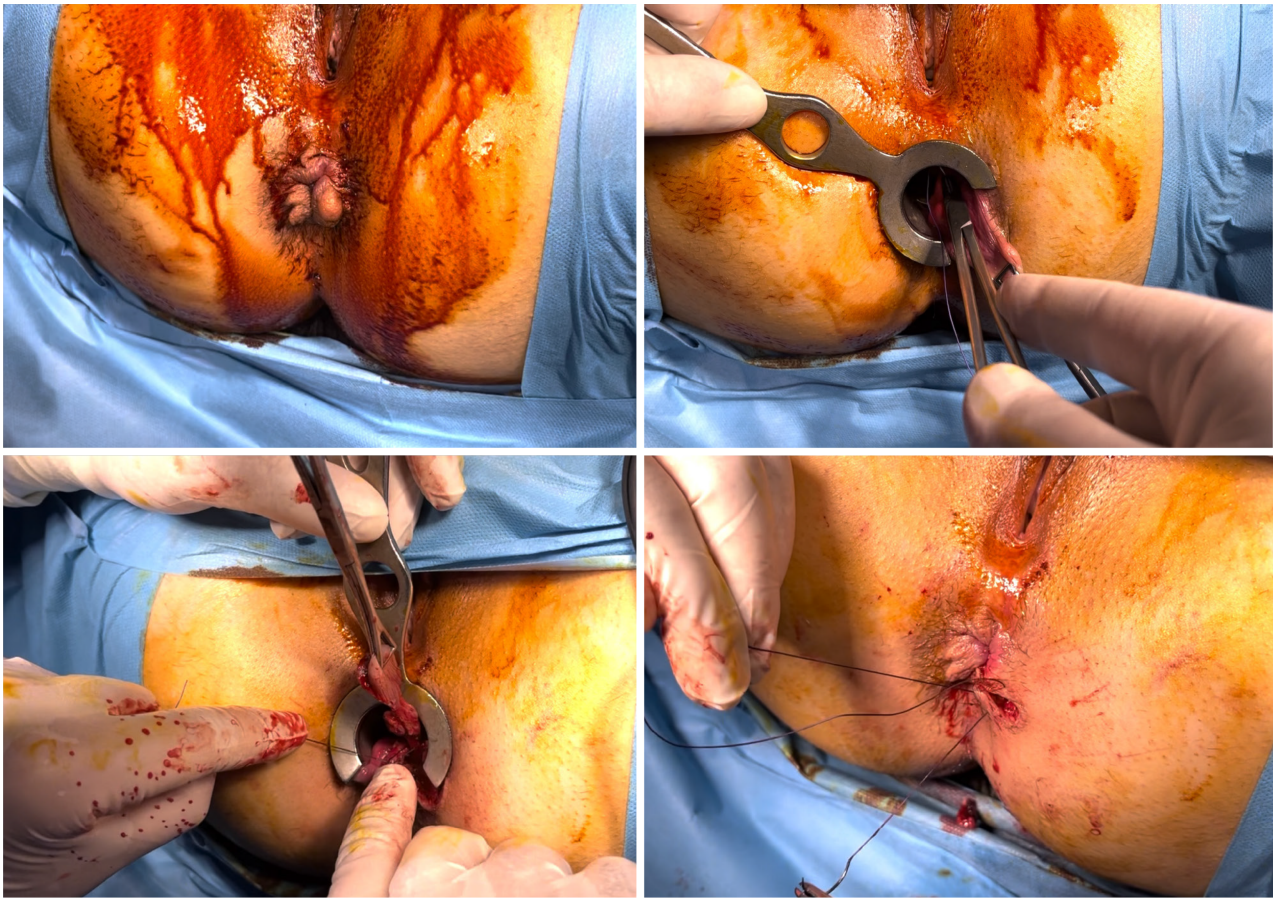

Figure 1 Ferguson hemorrhoidectomy.

RESULTS

A total of 45 consecutive patients were enrolled in the study. Of these patients, 75.6% (n = 34) were male, and 24.4% (n = 11) were female. In total, 53.3% (n = 24) of the patients underwent DG-HAL + FH, while 46.7% (n = 21) underwent FH. The demographic and clinical data are shown in Table 1.

The rate of intraoperative blood loss was lower in the DG-HAL + FH group (10 *vs* 20 mL, P = 0.004), and the days needed for postoperative analgesics were lower (2 *vs* 4 days, P < 0.05). The first and seventh-day VAS scores were similar in both groups. Clavien-Dindo Score-1 complications were higher in the DG-HAL + FH group (20.8% *vs* 9.5%), and most of them were urinary retention (16.7% *vs* 4.8%), but these were not statistically significant. The time to return to normal activities was higher in the DG-HAL + FH group (9.5 *vs* 6 days, P < 0.05). Recurrence occurred in four of the DG-HAL + FH group, but there was no recurrence in the FH group. Operative and postoperative follow-up data are shown in Table 2. There was no anal stenosis or incontinence in follow-up.

DISCUSSION

In the contemporary treatment of hemorrhoidal disease, there is a broad spectrum of methods ranging from conservative treatments to stapled hemorrhoidopexy. Excisional hemorrhoidectomy procedures are still the preferred treatment methods for grade 3-4 hemorrhoidal disease; however, they have specific adverse effects. Anal stenosis, incontinence, and postoperative pain, particularly after multiple excisions, can be troublesome for both the patient and the surgeon. Combined methods may help to prevent these undesirable side effects. Although limited literature studies have compared DG-HAL with stapled hemorrhoidopexy or mucopexy combinations, no study has compared DG-HAL + FH with FH. This study compared the reference close hemorrhoidectomy procedure Ferguson approach with combined DG-HAL + FH, and it was concluded that adding DG-HAL to FH resulted in less operative bleeding and a lower postoperative analgesic requirement.

Postoperative bleeding is a common and troublesome complication following hemorrhoidal surgery, typically categorized as either immediate or delayed [12,17,18]. A systematic review involving about 2000 patients showed that there was significantly less intra- and postoperative bleeding compared to the open technique[19]. Similarly, a meta-analysis comparing DG-HAL with stapled hemorrhoidectomy found a lower rate of postoperative bleeding in the DG-HAL group[20]. Another meta-analysis reported no significant difference in bleeding rates between DG-HAL and FH (OR: 0.41; 95%CI: 0.16, 1.05; Z = 1.87; P = 0.06)[21]. Therefore, incorporating interventions that have been proven

Table 1 Demographic and clinical results

		DG-HAL + hemorrhoidectomy (*n* = 24)	Ferguson hemorrhoidectomy (*n* = 21)	*P* value
Age		51.9 ± 13.7	45.1 ± 14.1	0.08
Gender	Male	18 (75.0)	16 (76.2)	0.63
	Female	6 (25.0)	5 (23.8)	

Numerical values are presented as mean ± SD. Categorical values are presented as *n* (%). DG-HAL: Doppler-guided hemorrhoidal artery ligation.

Table 2 Operative details and follow-up results

		DG-HAL + hemorrhoidectomy (*n* = 24)	Ferguson hemorrhoidectomy (*n* = 21)	*P* value
Intraoperative blood loss (mL)		10 (10-90)	20 (20-80)	0.004
Hospital stays duration (days)		1 (1-3)	1 (1-4)	0.08
Day 1 VAS score		2 (0-8)[a]	2 (0-10)[a]	0.06
Day 7 VAS score		0 (0-8)	0 (0-8)	0.85
Postoperative analgesic need (days)		2 (1-10)	4 (2-12)	0.02
Return to normal activity (days)		9.50 (4.00-20.00)	6.00 (1.00-20.00)	0.02
Postoperative complications	Yes	5 (20.8)	2 (9.5)	0.29
	No	19 (79.2)	19 (90.5)	
Complication	Urinary retention	4 (16.7)	1 (4.8)	0.45
	Tenesmus	1 (4.2)	1 (4.8)	
	None	19 (79.2)	19 (90.5)	
Clavien-Dindo Score	0	19 (79.2)	19 (90.5)	0.29
	1	5 (20.8)	2 (9.5)	
Recurrence	Yes	4 (16.7)	0 (0)	0.111
	No	20 (83.3)	21 (100)	

[a]$P < 0.05$ in Wilcoxon Signed-rank test compared to day 7.

Numerical values are presented as mean ± SD or median (min-max). Categorical values are presented as *n* (%). DG-HAL: Doppler-guided hemorrhoidal artery ligation; VAS: Visual Analog Scale.

beneficial in classical hemorrhoidectomy can reduce postoperative bleeding. In our series, we observed a significant difference in the rate of intraoperative bleeding between both groups.

The primary factor driving the search for alternative treatments following classical excision-based methods for hemorrhoidal disease is postoperative pain. Despite their cost, the development and preference for techniques such as DG-HAL are largely due to their ability to reduce pain[2]. Pain, although subjective and individual-specific, is often assessed using the validated VAS, a widely accepted method in current studies[22]. In a study by Lim *et al*[12], compared with the DG-HAL +/- laser hemorrhoidoplasty, no significant clinical or statistical difference was found in pain scores between the groups, as both are minimally invasive and non-excisional procedures. Poskus *et al*[13] have reported that both laser and mucopexy, when compared to excisional hemorrhoidectomy, were associated with lower postoperative pain scores. In a study by Long *et al*[5], when comparing the FH with the Milligan-Morgan Hemorrhoidectomy (MMH) + non-Doppler HAL, the MMH + non-Doppler HAL group had lower VAS scores at first defecation and at various postoperative intervals (12 hours, 1 day, 2 days, 3 days, and 7 days) and consumed fewer analgesics within 7 days compared to the FH group ($P < 0.05$), suggesting that MMH + NDG-HAL effectively alleviates surgical incision pain and reduces the need for analgesics. Based on these studies, it can be inferred that combined methods could potentially reduce pain. In our study, DG-HAL reduced the need for postoperative analgesia use compared to the FH group. This may be due to less surgical trauma in the DG-HAL group.

Another critical aspect in the selection of a treatment for hemorrhoidal disease is the time to return to daily activities, which is as important as pain and bleeding. While return-to-work times can extend up to a week following conventional methods, non-excisional procedures have reduced this period to as short as one day. The rapid return to work and quicker healing offered by minimally invasive methods compared to excisional methods are reasons for their preference

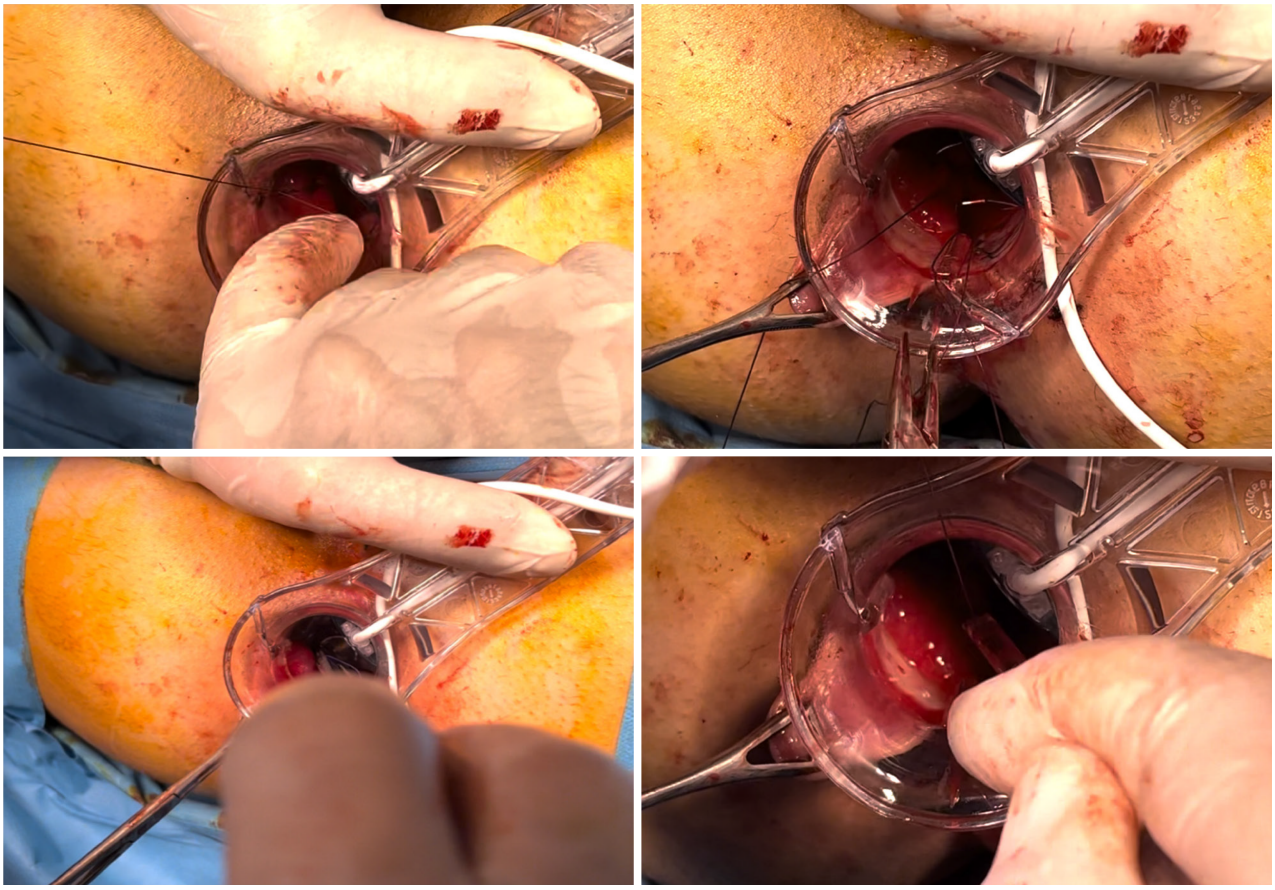

Figure 2 Doppler-guided hemorrhoidal artery ligation + hemorrhoidectomy with Angiodin-procto by Comepa.

[3,23]. The duration to resume daily activities is multifactorial, with postoperative pain and other complications being key factors prolonging this period. In a study by Abdelhamid *et al*[3], patients who underwent minimally invasive procedures such as combined hemorrhoidal artery ligation, returned to their daily activities sooner than those who had a FH. Similarly, Brusciano *et al*[24] showed this was associated with an earlier return to daily activities. Furthermore, Poskus *et al*[13] reported that both laser and mucopexy were associated with an earlier return to work compared to surgical excision. In contrast, our study did not show an early return-to-work advantage. This difference may be due to various factors, including the edema and/or inflammation in the rectal mucosal and submucosal layers caused by mucopexy, which can still be managed effectively with anti-inflammatory drugs and analgesics[24].

The most common postoperative complication is acute urinary retention, with rates up to 20%[25-27]. In our study, the urinary retention rate was similar in both groups. Adding DG-HAL to FH created a minimal increase in urinary retention but did not create a statistical difference. This may be due to the slightly longer operative duration of the DG-HAL + FH procedure or larger anoscope diameter, which may result in more significant sympathetic–parasympathetic nerve discordance. However, it is not easy to provide evidence to confirm this. This needs to be further investigated in more extensive patient series.

The effect of choosing combined methods on the long-term results should also be discussed. We observed more recurrences in the combined method. A randomized controlled trial by Aigner *et al*. compared DG-HAL with suture mastopexy *vs* suture mucopexy alone in treating grade III hemorrhoids. They examined 40 patients in two groups and found that patients who received DG-HAL had less pain but a higher long-term recurrence rate (10% *vs* 5%; $P = 0.274$) [28]. This was similar to the results of our study. On the other hand, there are contrary data about the recurrence rate, such as the randomized study which compared open hemorrhoidectomy with Doppler-guided hemorrhoid dearterialization and mucopexy; the results after a 1-year follow-up did not show any difference in relapse between the two groups [25].

The purpose of choosing the combined treatment was to avoid the unwanted complications of conventional hemorrhoidectomies, such as pain and anal stenosis, and to prevent unnecessary tissue and sensory loss. As the literature suggests that methods such as DG-HAL alone may be insufficient for grade 4 hemorrhoids, we have not yet started routinely applying them to grade 4, but we choose minimally invasive procedures in lower stages (DG-HAL alone for grade 2 disease and DG-HAL + FH for grade 3). As our case series grows, new results may lead us to return to the classical surgical method or suggest standardization of combined methods. In any case, developing new techniques or procedures in treating hemorrhoidal disease is essential due to the lack of a standardized technique.

Limitations

Our study, being single-centered and retrospective, has its limitations. Retrospective studies are inherently prone to bias as confounding variables may not be equally distributed across groups. However, we believe that the scarcity of data in the existing literature making the same comparisons as our research is a significant advantage in our favor. According to Goligher, internal hemorrhoidal disease is divided into four stages. However, the fact that hemorrhoidal disease can be seen in different stages in the same patient may limit the standardization of surgical techniques. The findings from this study should be interpreted in the context of the limitations mentioned in the Discussion. They should be verified in future studies with larger sample sizes and randomized controlled trials.

CONCLUSION

Our study concluded that combining DG-HAL with FH may result in less intraoperative bleeding and less postoperative analgesia use.

FOOTNOTES

Author contributions: Eray IC was responsible for conception, acquisition of data, drafting the article, final approval; Topal U was responsible for conception, analysis, and interpretation of data, revising the article, final approval; Gumus S was responsible for conception, revising the article, final approval; Isiker K was responsible for conception, acquisition of data, final approval; Yavuz B was responsible for data analysis, revising the article, final approval; Aydın I was responsible for conception and design, drafting the article, final approval.

Institutional review board statement: This study was conducted with the approval of the Cukurova University Faculty of Medicine Ethics Committee, as evidenced by decision number 138/31, dated 03 November, 2023. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent statement: Informed consent was obtained from all individual participants included in the study. Each participant was provided with comprehensive information regarding the nature of the study, the procedures involved, potential risks and benefits, and their rights as research subjects, including the right to withdraw from the study at any point without any consequences.

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ORIGINAL ARTICLE

Clinical Trials Study

Follow-up of elderly gastric cancer post-radical surgery: Trauma, complications, and prognosis

Li-Ling Zhu, Rui-Zhi Shen

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Abstract

BACKGROUND

The incidence of gastric cancer in the elderly is increasing; however, standardized surgical approaches are lacking.

AIM

To investigate the effects of radical surgery on the trauma response, postoperative complications, and long-term prognosis in elderly patients with gastric cancer.

METHODS

Between January 2020 and December 2023, 110 gastric cancer patients admitted to the Department of Oncology Jiangnan University Medical Center were categorized into a control group (40 cases) and an observation group (70 cases) based on surgical method differences. The control and observation group received palliative surgery and radical surgery, respectively, and were further divided into open (25 cases) and laparoscopic (45 cases) surgery. Surgical outcomes, trauma indicators, complication rates, and long-term survival at 6 months, 1-, and 2-years were compared.

RESULTS

Laparoscopic surgery showed superior surgical outcomes compared to the open surgery and control groups ($P < 0.05$). Trauma indicators were lowest in the laparoscopic group and highest in the control group ($P < 0.05$). No significant difference was observed in the complication rates between the open and laparoscopic groups ($P > 0.05$), but both were higher than those in the control group ($P < 0.05$). No significant differences were found in survival rates at different follow-up periods between the laparoscopic and open groups ($P > 0.05$); however, both groups showed higher survival rates than the control group ($P < 0.05$).

CONCLUSION
Radical surgery in elderly patients with gastric cancer reduces surgical trauma response, facilitates postoperative recovery, and improves long-term survival rates, albeit with an increased risk of complications. Laparoscopic radical surgery further minimizes postoperative trauma, with no significant difference in complication rates and survival prognosis compared with open radical surgery.

Key Words: Radical surgery; Elderly gastric cancer; Trauma stress response; Complications; Long-term prognosis

Core Tip: Although elderly patients have reduced surgical tolerance, surgery remains the primary treatment for gastric cancer in this population. Selecting appropriate surgical methods can reduce mortality and enhance the quality of life in elderly patients with gastric cancer.

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INTRODUCTION

The elderly, characterized by diminished antitumor cell proliferation and immune capabilities, are a high-incidence group for gastric cancer. With the aging of the population, the number of elderly gastric cancer patients has been increasing, with over 70% of patients aged 60 and above[1]. Radical surgery is the primary treatment for gastric cancer, effectively extending survival time. However, owing to the complex anatomical structure of the stomach, the risk of postoperative complications is high. Elderly patients often have multiple chronic systemic diseases that reduce surgical tolerance, increase the risk of complications, and affect postoperative recovery. Moreover, the limited life expectancy of older patients makes it difficult to achieve a significant increase in survival after radical surgery. There is an ongoing debate in the clinical setting regarding the choice of surgical approach for elderly patients with gastric cancer. Because gastric cancer in the elderly is a significant public health issue that is expected to increase with the intensification of aging, identifying efficient and safe surgical methods is crucial to reduce mortality and extend survival[2]. Using patients from the Jiangnan University Medical Center as an example, we explored the efficacy of radical surgery in elderly patients with gastric cancer to provide a basis for clinical surgical decision-making. These findings are reported in this study.

MATERIALS AND METHODS

General information

Patient demographics revealed that the study population consisted of gastric cancer patients treated at the Oncology Department of Jiangnan University Medical Center from January 2020 to December 2023. A total of 110 patients were included in the study after applying the inclusion and exclusion criteria. The patients were categorized into a control group (n = 40) and an observation group (n = 70) based on differences in surgical approaches. The observation group was further divided into laparoscopic (n = 45) and open surgery (n = 25) subgroups.

Control group: Male: 19; Female: 21. Age: 67-81 years (mean 75.31 ± 5.54). Tumor node metastasis (TNM) staging: IB-IIA (10 cases), IIB-IIIA (17 cases), and IIIB-IIIC (13 cases). Pathological examination revealed adenocarcinoma (34 cases), mucinous adenocarcinoma (four cases), and signet ring cell carcinoma (two cases).

Open surgery group: Male: 13; Female: 12. Age: 65-83 years (mean 75.55 ± 5.21). Pathology: Adenocarcinoma (20 cases), mucinous adenocarcinoma (4 cases), and signet ring cell carcinoma (1 case). TNM staging: IB-IIIA (15 cases), IIB-IIIA (six cases), and IIIB-IIIC (four cases).

Laparoscopic group: Male: 21; Female: 24. Age: 67-80 years (mean 75.43 ± 5.18). Pathological examination revealed adenocarcinoma (27 patients), mucinous adenocarcinoma (14 patients), and signet ring cell carcinoma (4 patients). The TNM staging: IIB-IIIA (21 cases), IIB-IIIA (17 cases), and IIIB-IIIC (7 cases). No statistically significant differences were found in the baseline characteristics among the three groups (P > 0.05), making them eligible for the study.

The inclusion criteria: (1) Diagnosis of gastric cancer according to standard criteria; (2) Age 60 years; (3) No distant metastasis; (4) No previous radiotherapy, chemotherapy, or immunotherapy; (5) No cognitive or communication

impairments were observed; and (6) Informed consent was obtained from all patients and their families.

The exclusion criteria: (1) Other concurrent malignancies; (2) Inability to tolerate surgery; (3) Other functional or structural organ impairments; (4) History of abdominal surgery; (5) Immunological disorders; (6) Coagulation dysfunction; and (7) Death from non-tumor-related causes or withdrawal during follow-up.

Surgical methods

The control group was treated with palliative surgery: Patients in the control group underwent palliative surgery, which was initiated with the patient in the supine position under general anesthesia and endotracheal intubation. A midline laparotomy incision was made, and the tumor location, size, and metastatic status were assessed using a systematic approach from the periphery to the center. Palliative surgical options include resectional techniques such as total, proximal, and distal gastrectomy and non-resectional techniques such as jejunostomy.

The observation group was treated with radical surgery interventions: Open surgery subgroup: Patients who underwent conventional open radical gastrectomy with the same anesthetic and positioning protocols as the control group. An incision from the xiphoid process to the umbilicus allows for exploration and vascular control of the gastric area. The stomach was mobilized and the omentum was transected using electrocautery. Lymph node dissection was performed sequentially, followed by resection of the stomach containing the tumor and anastomosis of the stomach and duodenum using standard techniques, such as Billroth I or II, culminating in routine wound closure.

Laparoscopic group underwent laparoscopic radical gastrectomy for gastric cancer: The patients were positioned in a supine position with the head lower than the feet, with legs abducted approximately 30° in a 'big' character shape, and the left leg was bent in a 'jackknife' manner at approximately 15°. Endotracheal intubation was performed and general anesthesia was administered. The skin on the patient's gastric wall was secured and punctured to create an artificial pneumoperitoneum. Punctures were made at the umbilical hole, 5 mm to the left of the umbilicus, along the anterior axillary line at the costal margin, and at the right midclavicular line (at the same horizontal level as the umbilicus) to serve as operative ports. Ultrasonic scalpels and other instruments were inserted through the surgical ports. Under laparoscopic visualization, the right gastroepiploic vessels were clamped and the left and right gastric arteries were ligated to interrupt the gastric branches. The mesentery and greater omentum were stripped and the lymph nodes were cleared. A 5 cm incision was made in the midline of the patient's abdomen, and the duodenum was transected. The surgeon used intestinal forceps to grasp the gastric remnant and proximal jejunum and lifted the stomach out of the abdominal cavity. The stomach was transected using a stapler (the transection site was 5 cm from the cancerous lesion). The jejunum was removed from the abdominal cavity and holes were drilled at the mesenteric edge of the greater curve of the stomach and jejunum. A stapler was used to anastomose the stomach and jejunum, followed by routine suturing.

Patient general information survey

Surgical-related indicators: Operative time, intraoperative blood loss, time to first flatus postoperatively, time to ambulation, and length of postoperative hospital stay were recorded for all three patient groups.

Trauma stress response: Fasting venous blood (5 mL) was collected from patients in all groups preoperatively and 12 hours postoperatively, followed by centrifugation to obtain the serum. Measure serum levels of endothelin (ET), nitric oxide (NO), and C-reactive protein (CRP) using an enzyme-linked immunosorbent assay with kits from Shanghai Lanjing Biotech Co., Ltd., strictly according to the manufacturer's instructions.

Complications: Monitor and document the incidence of postoperative complications in the two groups including anastomotic leakage, incision infection, pulmonary infection, dumping syndrome, and intra-abdominal infection.

Long-term prognosis follow-up survey: Follow-up surveys were conducted *via* telephone and outpatient reviews after patient discharge until recurrence or death. The survival rates of the two groups were recorded at 6 months, 1 year, and 2 years after discharge.

Statistical analysis

Data were analyzed using statistical product and service solutions 20.0 software. Quantitative data conforming to a normal distribution are presented as mean ± SD, with *t*-tests for comparisons and F-tests for multiple group comparisons. Qualitative data are expressed as frequency and percentage *n* (%), with χ^2 tests for analysis; $P < 0.05$ indicating statistical significance.

RESULTS

Surgical-related metrics

Patients in the open laparotomy group exhibited lower intraoperative blood loss and shorter temporal metrics than those in the control group. The laparoscopic group demonstrated intraoperative blood loss lower than that of the open laparotomy group, and the remaining four temporal metrics were at their lowest levels ($P < 0.05$). See Table 1.

Table 1 Comparison of surgical-related indicators among three groups of patients, mean ± SD

Groups	Cases (*n*)	Intraoperative blood loss (mL)	Surgery duration (minute)	Postoperative time to first flatus (day)	Time to ambulation (day)	Postoperative hospital stay (day)
Control	40	398.14 ± 74.21	301.25 ± 45.15	5.25 ± 1.31	3.94 ± 1.21	16.91 ± 4.23
Open surgery	25	205.13 ± 69.32	265.13 ± 37.43	4.13 ± 1.15	3.06 ± 0.80	15.15 ± 3.71
Laparoscopic surgery	45	177.31 ± 55.15	231.25 ± 27.77	3.43 ± 1.02	2.87 ± 0.74	13.15 ± 3.15
F value		131.998	37.756	26.156	14.486	10.973
P value		0.000	0.000	0.000	0.000	0.000

Quantitative data were compared across multiple groups using the *F*-test.

Trauma stress response

In the comparison of stress response indicators among the three groups, the control group exhibited the highest levels of ET, NO, and CRP, while the laparoscopic group showed the lowest levels of stress indicators ($P < 0.05$). See Table 2.

Incidence of complications

The incidence of complications in the control group was significantly lower than that in both radical surgery groups ($P < 0.05$), and there was no statistically significant difference in the incidence of complications between the open and laparoscopic surgery groups ($P > 0.05$). See Table 3.

Long-term prognosis follow-up survey

At the three postoperative follow-up time points, there was no statistically significant difference in survival rates between the open and laparoscopic groups ($P > 0.05$). At each of the three follow-up time points, the control group had the lowest survival rates ($P < 0.05$). See Table 4.

DISCUSSION

China's aging population has led to an increase in the number of elderly patients with gastric cancer. Despite medical advancements, a universal cure for gastric cancer remains elusive. Surgery, particularly radical surgery, is one of the primary treatments for prolonging life and removing cancerous lesions, and has shown significant efficacy[3]. However, elderly patients often have reduced physical reserves and lower tolerance to surgery, leading to higher risks and prolonged recovery times, which can increase medical costs and potentially reduce prognosis.

This study analyzed 110 elderly patients with gastric cancer who underwent palliative, open radical, or laparoscopic radical surgery. The palliative surgery group exhibited the highest blood loss and longest time indicators (surgery duration, first flatus, ambulation, and hospital stay) ($P < 0.05$), indicating greater trauma and prolonged recovery compared to the radical surgeries. Radical surgeries employ sharp dissection principles, reducing the handling of vascular branches, thus decreasing blood loss[4]. In contrast, palliative surgeries that do not aim for complete lesion removal involve more extensive dissection of tumor interfaces, which increases blood loss and operation time[5].

Compared with conventional surgical approaches, laparoscopic surgery, aided by visualization through a lens, effectively addresses the technical challenge of obtaining a clear view of the lesion, which is often difficult using traditional methods. The laparoscopic group showed lower stress response indicators than the open group, with the control group showing the highest levels ($P < 0.05$). ET, NO, and CRP are key indicators of the stress response, with ET and NO levels positively correlated with traumatic stress, and CRP is rapidly released after tissue damage[6-8]. Palliative surgery induces a stronger stress response owing to longer operation times and greater blood loss, whereas laparoscopic radical surgery, which is minimally invasive, reduces surgical trauma and stress levels[9,10].

The palliative surgery group had a lower incidence of complications than the radical surgery groups ($P < 0.05$), with no significant difference between the laparoscopic and open radical surgery groups ($P > 0.05$). Palliative surgery, aimed at improving symptoms without complete tumor removal, preserves more vascular tissue, leading to better blood supply, faster mucosal regeneration, and reduced risk of infection[11,12]. Anastomotic leakage, a common complication of gastrointestinal surgery, is mitigated by palliative surgery because of the enhanced blood supply and reduced inflammatory mediator secretion[13]. However, the technical challenges of laparoscopic lymph node dissection and anastomosis may affect the quality of the surgery and increase the risk of complications if not performed correctly.

Studies have increasingly indicated that patients with gastric cancer who undergo radical-intent gastrectomy after responding to several regimens of combined chemotherapy can achieve good survival outcomes. This study found that, compared with radical surgery, the palliative surgery group had lower survival rates at 6 months, 1 year, and 2 years postoperatively ($P < 0.05$), while there was no significant difference between the laparoscopic and open radical surgery

Table 2 Comparison of trauma stress response indicators among three groups of patients, mean ± SD

Groups	Cases (*n*)	ET (ng/L)		NO (μmol/L)		CRP (mg/L)	
		Before	After 12 hours	Before	After 12 hours	Before	After 12 hours
Control	40	1.05 ± 0.32	1.80 ± 0.58	10.08 ± 3.17	20.13 ± 3.40	21.15 ± 1.21	63.12 ± 12.58
Open surgery	25	1.04 ± 0.39	1.65 ± 0.53	10.11 ± 3.15	18.05 ± 2.45	21.30 ± 1.25	59.12 ± 11.37
Laparoscopic surgery	45	1.01 ± 0.35	1.39 ± 0.51	10.03 ± 3.11	16.13 ± 2.11	21.34 ± 1.18	50.10 ± 10.33
F value		0.149	6.232	0.006	22.925	0.279	14.367
P value		0.862	0.002	0.994	< 0.001	0.757	< 0.001

Quantitative data were compared across multiple groups using the *F*-test. ET: Endothelin; NO: Nitric oxide; CRP: C-reactive protein.

Table 3 Comparison of complication incidence rates among three groups of patients, *n* (%)

Groups	Cases (*n*)	Anastomotic fistula	Incision infection	Pulmonary infection	Dumping syndrome	Abdominal infection	Total incidence
Control	40	2 (5.00)	3 (7.50)	0 (0)	1 (2.50)	2 (5.00)	8 (20.00)
Open surgery	25	3 (12.00)	4 (16.00)	1 (4.00)	2 (8.00)	4 (16.00)	14 (56.00)
Laparoscopic surgery	45	7 (15.56)	1 (2.22)	0 (0)	5 (11.11)	5 (11.11)	18 (40.00)
Control and laparoscopic group χ^2/P value							8.904/0.002
Control and laparoscopic group χ^2/P value							3.989/0.045
Control and laparoscopic χ^2/P value							1.657/0.197

Qualitative data are presented as frequencies and percentages and were analyzed using the χ^2 test.

Table 4 Comparison of long-term prognosis follow-up survey among three groups of patients, *n* (%)

Group	Cases (*n*)	6 months post-discharge	1 year after discharge	2 years after discharge
Control	40	36 (90.00)	28 (70.00)	22 (55.00)
Open surgery	25	24 (96.00)	23 (92.00)	20 (80.00)
Laparoscopic surgery	45	44 (97.78)	41 (91.11)	34 (75.56)
Control and open χ^2/P value		0.780/0.377	4.406/0.035	4.205/0.040
Control and laparoscopic χ^2/P value		2.313/0.128	6.176/0.012	3.980/0.046
Open and laparoscopic χ^2/P value		0.183/0.668	0.016/0.898	0.180/0.671

Qualitative data are presented as frequencies and percentages and were analyzed using the χ^2 test.

groups ($P > 0.05$). Radical surgery effectively removes potentially metastatic lymph nodes and infiltrated tissues, thereby reducing the risk of tumor cell spread and residual lesions[14-17].

CONCLUSION

Palliative surgery in elderly patients with gastric cancer is associated with more severe traumatic impact and extended recovery period. Notably, the incidence of postoperative complications is lower after curative surgery. Conversely, curative surgery is associated with improved long-term survival rates. The use of laparoscopic techniques for curative procedures further mitigate surgical trauma. However, our data indicate that this minimally invasive approach does not significantly influence the rate of postoperative complications or the long-term survival outcomes in these patients. In

summary, this study provides specific recommendations and references for clinicians when selecting surgical approaches for elderly patients with gastric cancer, thereby enhancing the clinical applicability of this research.

FOOTNOTES

Author contributions: Zhu LL designed the study; Zhu LL and Shen RZ analyzed the data, involved in the data collection and writing of this article; All the authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Patient selection and operative strategies for laparoscopic intersphincteric resection without diverting stoma

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Abstract

BACKGROUND

Diverting stoma (DS) is routinely proposed in intersphincteric resection for ultra-low rectal cancer, but it is associated with increased stoma-related complications and economic burden. Appropriate patient selection and operative strategies to avoid stoma formation need further elucidation.

AIM

To select patients who may not require DS.

METHODS

This study enrolled 505 consecutive patients, including 84 who underwent stoma-free (SF) intersphincteric resection. After matching, patients were divided into SF (n = 78) and DS (n = 78) groups. The primary endpoint was the anastomotic leakage (AL) rate within 6 months and its protective factors for both the total and SF cohorts. The secondary endpoints included overall survival and disease-free survival.

RESULTS
The AL rate was greater in the SF group than in the DS group (12.8% *vs* 2.6%, $P = 0.035$). Male sex [(odds ratio (OR) = 2.644, $P = 0.021$], neoadjuvant chemoradiotherapy (nCRT) (OR = 6.024, $P < 0.001$), and tumor height from the anal verge ≤ 4 cm (OR = 4.160, $P = 0.007$) were identified as independent risk factors. Preservation of the left colic artery (LCA) was protective in both the total cohort (OR = 0.417, $P = 0.013$) and the SF cohort (OR = 0.312, $P = 0.027$). The female patients who did not undergo nCRT and had preservation of the LCA experienced a significantly lower incidence of AL (2/97, 2.1%). The 3-year overall survival or disease-free survival did not significantly differ between the groups.

CONCLUSION
Female patients who do not receive nCRT may avoid the need for DS by preserving the LCA without increasing the risk of AL or compromising oncological outcomes.

Key Words: Anastomotic leakage; Diverting stoma; Laparoscopic intersphincteric resection; Ultralow rectal cancer

Core Tip: This study aimed to investigate suitable patient selection and operative strategies by comparing the surgical results and oncological outcomes between stoma-free and diverting stoma intersphincteric resection. Our study makes a significant contribution to the literature because we found female patients without neoadjuvant chemoradiotherapy could be exempted from diverting stomas by preserving the left colic artery without compromising anastomotic leakage risk and oncological outcomes.

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INTRODUCTION

Intersphincteric resection (ISR) is a sphincter-preserving surgical technique designed to maintain anal function in patients with ultralow rectal cancers. However, anastomotic leakage (AL) is a serious complication associated with laparoscopic ISR (Ls-ISR), leading to prolonged hospital stays, severe abdominal infections, the need for permanent stomas, and even mortality[1-6]. AL is a multifactorial complication that is particularly prevalent in patients with tumors located in the lower rectum, which has a relatively high incidence risk[7-9]. Diverting the bowel contents can help prevent mechanical pressure and fecal contamination at the anastomotic site. This intervention reduces the risk of AL, which is associated with severe clinical symptoms and the need for reoperation[10,11].

A diverting stoma (DS) is a double-edged sword. Although it reduces the risk of AL and associated complications, it also has significant disadvantages, including peristomal inflammation, stoma prolapse, delayed closure, and the possibility of a permanent stoma. Moreover, a second operation to close the stoma can lead to further surgical complications, such as surgical site infection, bowel obstruction, and even leakage. These complications prolong hospital stays and increase medical costs, adding to the patient burden[11-17].

The effects of DS on anal function and long-term oncological outcomes also warrant further investigation. However, few studies have focused on selecting a cohort of patients with a low risk of AL who could undergo Ls-ISR for ultralow rectal cancer without DS. Identifying such a cohort could reduce the stoma rate without increasing the risk of AL, thereby decreasing the economic burden, minimizing stoma-related complications, and ultimately improving the quality of life for these patients. We conducted a large retrospective case-matched cohort study to evaluate the short-term and oncological outcome of Ls-ISR without DS. Additionally, we aimed to identify patients with a low risk of AL in whom stomas might be safely eliminated.

MATERIALS AND METHODS

Patients

We retrospectively collected data from patients with ultralow rectal cancer who underwent Ls-ISR at a single center between January 2012 and June 2023. The inclusion criteria were as follows: (1) Ultralow rectal cancer with tumors located less than 5 cm from the anal verge (AV); (2) Ls-ISR surgery; and (3) Radical resection of the tumor. The exclusion criteria were as follows: (1) Abdominoperineal resection or Hartmann's procedure; and (2) Combined organ resection.

Multidisciplinary team meetings determined the treatment strategies for each patient, including the need for neoadjuvant chemoradiotherapy (nCRT). Our preferred approach was a long course of preoperative chemoradiotherapy based on 5-fluorouracil, with a radiation protocol of 45 Gy in 25 fractions followed by a 5.4 Gy boost, for a total of 50.4 Gy.

In total, 505 consecutive patients were enrolled in this study (Figure 1). Complications were defined as grade II or higher according to the Clavien-Dindo classification. All patients provided written informed consent. This study was approved by the Ethics Committee of Peking University First Hospital (2020149).

Surgical procedures

The transabdominal team conducted a standard total mesorectal excision, ensuring careful preservation of the bilateral hypogastric nerves and associated neurovascular bundles. The dissection followed the intersphincteric plane between the puborectalis muscle and the internal anal sphincter and was performed with precision and direct visualization. Meanwhile, the perineal team accessed the anus, dilated the anal canal to approximately three finger widths, and employed a Lone Star retractor to expose the inferior tumor margin. To prevent the spread of cancer cells, the rectum and anal canal were irrigated with povidone-iodine.

After closing the anal orifice at least 1 cm below the tumor, the internal sphincter was circumferentially incised, and dissection along the intersphincteric plane was conducted. This dissection continued cephalad to connect with the transabdominal team. Upon removing the distal rectum through the anus, the sigmoid colon was transected 15 cm above the superior tumor margin, and the specimen was extracted. The surgical site was then irrigated with a 5% iodophor solution.

A coloanal anastomosis was subsequently performed. Intraoperative frozen-section pathology was usually necessary to verify the distal resection margin status if it was less than 1 cm or potentially positive. The decision to perform a DS was made by the surgeon in consultation with the patient during the procedure. If a DS was indicated, a loop ileostomy was created in the right lower abdomen.

Diagnosis and grading of anastomosis leakage

Diagnosis was made based on clinical symptoms, such as pain, fever, tachycardia, peritonitis, or abnormal drainage, and radiological findings, such as fluid- or gas-containing collections observed on CT scans. The ISGRC grading system was used to assess the severity of AL as follows[18]: Grade A refers to radiological leakage that is asymptomatic and does not necessitate any intervention; grade B involves leakage that requires active management but does not require surgical reoperation, such as the use of antibiotics or radiological/endoscopic interventions; and Grade C signifies a severe leakage that mandates reoperation.

Data collection and follow-up

We collected basic clinical and pathological characteristics of patients, including sex, age, body mass index (BMI), nCRT, diabetes status, American Society of Anesthesiologists score, tumor distance from the AV, differentiation status, maximal tumor diameter, (y) pT stage, (y) pN stage, (y) pTNM stage (American Joint Committee on Cancer, 8th edition), and AL. We also recorded perioperative outcomes, including operative time, blood loss, conversion to open surgery, postoperative complications, reoperation, and mortality.

Follow-up was conducted every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. At each visit, patients underwent a physical examination, serum carcinoembryonic antigen level measurement, and abdominopelvic magnetic resonance imaging or CT.

Statistical analysis

The χ^2 test or Fisher's exact test was used to analyze differences between the primary and validation cohorts. Variables with a P value < 0.100 in the univariate analyses were included in the multivariate analyses. A greedy matching algorithm, with a caliper width equal to 0.20 of the standard deviation of the logit transformation of the estimated propensity score, was applied for propensity score matching (PSM)[19]. Propensity scores were estimated using variables such as sex, age, BMI, American Society of Anesthesiologists score, maximum tumor diameter, clinical (or pathological) stage, preoperative treatment, height of the anastomotic site from the AV, and left colic artery (LCA) retention. To avoid multicollinearity, the height of the lower edge of the tumor from the AV was not included in the models because it was correlated with the height of the anastomotic site from the AV. The estimated propensity score distribution was similar between the two groups, with no extreme outliers. The DS and stoma-free (SF) groups were matched at a 1:1 ratio using PSM.

Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using univariate and multivariate logistic regression analyses, with the AL rate as the outcome variable at a significance level of 5%. All the statistical analyses were two-sided, with statistical significance set at P < 0.05. R software (version 4.3.2) and SPSS software (version 25.0) were used for the statistical analyses.

RESULTS

Patient characteristics

A total of 505 patients, including 317 males (64.8%) and 188 females (35.2%), were analyzed. DS was performed on 421 patients (83.4%). The median age was 60 years (range 20-84) in the DS group and 64 years (range 23-84) in the SF group.

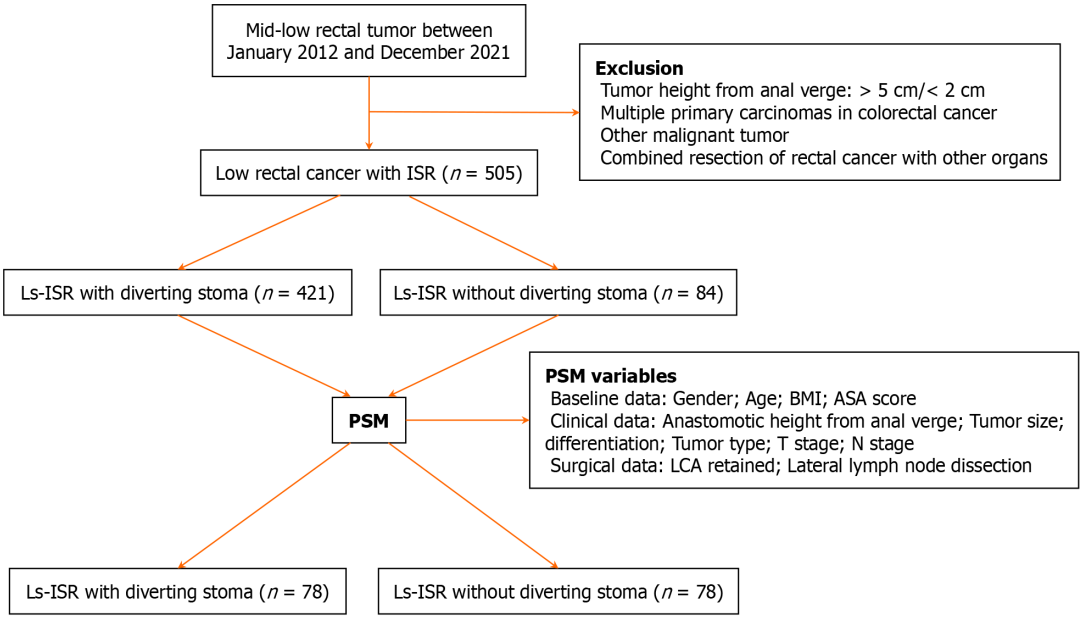

Figure 1 Flow chart. PSM: Propensity score matching; ISR: Intersphincteric resection; Ls-ISR: Laparoscopic intersphincteric resection; BMI: Body mass index; ASA: American Society of Anesthesiologists; LCA: Left colic artery.

In the baseline cohort (n = 505), the DS and SF groups significantly differed in terms of age over 60 years (51.6% *vs* 70.2%, P = 0.003), nCRT (14.7% *vs* 3.6%, P = 0.009), height of the tumor from the AV (4.0 cm *vs* 4.5 cm, P < 0.001), height of the anastomotic site from the AV (2.00 cm *vs* 2.50 cm, P < 0.001), and LCA retention (48.7% *vs* 72.6%, P < 0.001). The two groups did not significantly differ in terms of poor differentiation (P = 0.216), median maximal tumor size (P = 0.628), or TNM stage (P = 0.659).

After PSM at a 1:1 ratio, 156 patients (78 with DS and 78 with SF) were included. All variables were statistically balanced between the two groups after PSM (Table 1).

Perioperative outcomes in the DS and SF groups

Before PSM, the operative time in the DS group was longer than that in the SF group (172 min *vs* 171 min, P = 0.015). Although the total AL rate in the DS group was lower than that in the SF group, this difference was not statistically significant (7.6% *vs* 13.1%, P = 0.099). The rates of grade III postoperative complications (3.6% *vs* 9.5%, P = 0.035) and grade C AL (0.5% *vs* 6.0%, P < 0.001) significantly differed between the groups. Additionally, the DS group had a significantly higher completion rate of postoperative chemotherapy (86.8% *vs* 59.0%, P < 0.001) and a higher rate of permanent stoma (11.2% *vs* 2.3%, P < 0.001) than the SF group.

After PSM, significant differences were observed between the two groups in terms of grade III postoperative complications (2.6% *vs* 10.3%, P = 0.050) and total AL rates (2.6% *vs* 12.8%, P = 0.035). However, the incidence of grade C AL (0% *vs* 6.4%, P = 0.069) was not significantly different. The operative time (P = 0.109), completion rate of adjuvant chemotherapy (P = 0.738), or incidence of permanent stoma (P = 0.521) did not significantly differ after PSM.

The estimated blood loss, reoperation rate, postoperative hospital stay, and incidence of rectovaginal fistulas and anastomotic stricture did not differ between the two groups before and after PSM (Table 2).

Multivariate analyses of the risk factors for AL

In the univariable logistic regression analysis, male sex (OR = 2.883, 95%CI: 1.310-6.343, P = 0.009), BMI ≥ 25 kg/m² (OR = 1.899, 95%CI: 1.020-3.536, P = 0.043), and nCRT (OR = 4.805, 95%CI: 2.429-9.502, P < 0.001) were identified as risk factors for AL. The height of the tumor from the AV ≤ 4 cm (OR = 2.563, 95%CI: 0.986-6.658, P = 0.053) and LCA retention (OR = 0.068, 95%CI: 0.341-0.102, P = 0.105) did not significantly influence AL incidence. The use of DS (OR = 0.564, 95%CI: 0.273-1.167; P = 0.123) also showed no significant efficacy for AL prevention in the univariable analysis.

In the multivariable logistic regression analysis, AL-related covariates with P < 0.2 (sex, BMI, nCRT, LCA retention, DS, and height of the tumor from the AV), male sex (OR = 2.644, 95%CI: 1.161-6.020, P = 0.021), nCRT (OR = 6.024, 95%CI: 2.830-12.822, P < 0.001), and height of the tumor from the AV ≤ 4 cm (OR = 4.160, 95%CI: 1.488-11.634, P = 0.007) were identified as independent risk factors. Conversely, LCA retention (OR = 0.417, 95%CI: 0.209-0.830, P = 0.013) and DS (OR = 0.204, 95%CI: 0.087-0.481, P < 0.001) were found to be independent protective factors (Table 3).

Further analysis of the SF group revealed that LCA retention was a protective factor for AL in these patients, both in the univariate (OR = 0.393, 95%CI: 0.028-0.891, P = 0.039) and multivariate (OR = 0.312, 95%CI: 0.121-0.802, P = 0.027) analyses (Table 3).

Table 1 Clinical and surgical characteristics before and after matching

Variables	Before PSM		*P* value	After PSM		*P* value
	DS (*n* = 421)	SF (*n* = 84)		DS (*n* = 78)	SF (*n* = 78)	
Gender			0.042			0.521
Male	273 (64.8)	44 (52.4)		34 (43.6)	39 (50.0)	
Female	148 (35.2)	40 (47.6)		44 (56.4)	39 (50.0)	
Age, median (range) years	60.0 (20.0, 84.0)	64.0 (23.0, 84.0)	0.003	64.0 (31.0, 82.0)	64.0 (33.0, 84.0)	1
< 60	204 (48.4)	25 (29.8)		25 (32.1)	25 (32.1)	
≥ 60	217 (51.6)	59 (70.2)		53 (67.9)	53 (67.9)	
BMI, median (range) kg/m^2	23.7 (14.5, 32.9)	23.8 (17.8, 34.4)	1	23.9 (17.1, 29.3)	23.7 (17.8, 34.4)	1
< 25	270 (64.1)	54 (64.3)		51 (65.4)	52 (66.7)	
≥ 25	151 (35.9)	30 (35.7)		27 (34.6)	26 (33.3)	
ASA score			0.005			0.744
I-II	408 (96.9)	75 (89.3)		74 (94.9)	72 (92.3)	
III	13 (3.1)	9 (10.7)		4 (5.1)	6 (7.7)	
Diabetes			1			0.811
Yes	55 (13.1)	11 (13.1)		9 (11.5)	11 (14.1)	
No	366 (86.9)	73 (86.9)		69 (88.5)	67 (85.9)	
Tumor size, median (range) mm	35.0 (10.0, 120.0)	35.0 (15.0, 80.0)	0.628	35.0 (20.0, 90.0)	35.0 (15.0, 80.0)	0.958
> 35	209 (49.6)	41 (48.8)		32 (41.0)	36 (46.2)	
≤ 35	212 (50.4)	43 (51.2)		46 (59.0)	42 (53.8)	
Differentiation status			0.216			0.277
Poor	65 (15.4)	8 (9.5)		10 (12.8)	5 (6.4)	
Well-moderate	356 (84.6)	76 (90.5)		68 (87.2)	73 (93.6)	
Tumor type			0.944			1
Ulcer	281 (66.7)	57 (67.9)		57(73.1)	57(73.1)	
Protrusion	140 (33.3)	27 (32.1)		31(26.9)	31(26.9)	
pT stage			0.362			0.255
0-2	181 (43.0)	31 (36.9)		36 (46.2)	28 (35.9)	
3	240 (57.0)	53 (63.1)		42 (53.8)	50 (64.1)	
pN stage			0.782			0.104
N+	150 (35.6)	28 (33.3)		16 (20.5)	26 (33.3)	
N0	271 (64.4)	56 (66.7)		62 (79.5)	52 (66.7)	
M stage			1			1
M1	8 (1.9)	1 (1.2)		1 (1.3)	1 (1.3)	
M0	413 (98.1)	83 (98.8)		77 (98.7)	77 (98.7)	
pTNM stage			0.659			0.104
I-II	154 (36.6)	28 (33.3)		16 (20.5)	26 (33.3)	
III-IV	267 (63.4)	56 (66.7)		62 (79.5)	52 (66.7)	
nCRT			0.009			1
Yes	62 (14.7)	3 (3.6)		4 (5.1)	3 (3.8)	
No	359 (85.3)	81 (96.4)		74 (94.9)	75 (96.2)	
Tumor height from anal verge, median	4.0 (3.5-4.0)	4.5 (4.0-5.0)	< 0.001	4.0 (4.0-4.5)	4.0 (4.0-4.5)	0.412

(range) cm						
≤ 4.0	343 (81.5)	41 (48.8)		48 (61.5)	39 (50.0)	
> 4.0	68 (18.5)	43 (51.2)		30 (38.5)	39 (50.0)	
Anastomotic height from anal verge, median (range) cm	2.00 (0.50, 4.00)	2.50 (1.00, 4.00)	< 0.001	2.00 (1.00, 4.00)	2.50 (1.00, 4.00)	1
≤ 3.0	406 (96.4)	73 (86.9)		72 (92.3)	72 (92.3)	
> 3.0	15 (3.6)	11 (13.1)		6 (7.7)	6 (7.7)	
LCA retention			< 0.001			1
Yes	205 (48.7)	61 (72.6)		54 (69.2)	55 (70.5)	
No	216 (51.3)	23 (27,4)		24 (30.8)	23 (29.5)	
Lateral lymph node dissection			0.260			0.247
Yes	51 (12.1)	6 (7.2)		9 (11.5)	4 (5.1)	
No	370 (87.9)	78 (92.8)		69 (88.5)	74 (94.9)	
Hb (g/L)			0.911			0.802
≥ 120	366 (86.9)	74 (88.1)		70 (89.7)	68 (87.2)	
< 120	55 (13.1)	10 (11.9)		8 (10.3)	10 (12.8)	
ALB (g/L)			0.328			0.342
≥ 35.0	334 (79.3)	62 (73.8)		63 (80.8)	57 (73.1)	
< 35.0	87 (20.7)	22 (26.2)		15 (19.1)	21 (26.9)	
CEA (μg/L)			0.122			0.561
> 5.0	134 (31.8)	19 (22.6)		15 (19.2)	19 (24.4)	
≤ 5.0	287 (68.2)	65 (77.4)		63 (80.8)	59 (75.6)	

Data are presented as *n* (%). BMI: Body mass index; ASA: American Society of Anesthesiologists; nCRT: Neoadjuvant chemotherapy; LCA: Left colic artery; Hb: Hemoglobin; ALB: Albumin; PSM: Propensity score matching; DS: Diverting stoma; SF: Stoma-free; CEA: Carcinoembryonic antigen.

Long-term survival

The median follow-up period was 48 months. During this time, 8 patients in the DS group died, with 1-year, 2-year, and 3-year disease-free survival (DFS) rates of 98.7%, 97.2%, and 95.1%, respectively, and overall survival (OS) rates of 98.7%, 97.2%, and 97.2%, respectively. In the SF group, 6 patients died, with 1-year, 2-year, and 3-year DFS rates of 97.0%, 95.3%, and 91.1%, respectively, and OS rates of 97.0%, 95.3%, and 95.3%, respectively. The 3-year DFS (P = 0.588) or 3-year OS (P = 0.639) did not significantly differ between the DS and SF groups (Figure 2).

Patient selection and clinical decision for Ls-ISR without DS

Patients with the following characteristics were defined as a low-risk cohort for AL: Female patients without neoadjuvant therapy and patients with intraoperative preservation of the LCA. The clinical characteristics and outcomes of the high-risk and low-risk cohorts for AL were analyzed (Table 4). The low-risk cohort had an earlier pT stage (P = 0.014), shorter operative time (P = 0.006), and less blood loss (P = 0.003). In terms of postoperative outcomes, this low-risk cohort had a lower risk of postoperative complications than the high-risk cohort (P = 0.021). The AL rate in the low-risk cohort (2 of 97 patients) was significantly lower than the overall incidence of AL in the high-risk cohort (2.1% *vs* 10.3%, P = 0.010) and the baseline cohort (2.1% *vs* 8.5%, P = 0.027). Therefore, the clinical decision to perform Ls-ISR without a DS was found to be safe and feasible for this low-risk cohort. A clinical decision analysis chart is recommended for patients undergoing Ls-ISR surgery for low rectal cancer to assess the necessity of a stoma during the procedure (Figure 3).

DISCUSSION

ISR surgery combined with DS is considered the standard procedure for ultralow rectal cancer. DS is routinely performed to minimize the risk of AL and related complications by temporarily diverting bowel contents[10,11]. However, DS may increase the risk of permanent stoma, bowel obstruction, and renal insufficiency due to massive electrolyte loss as well as complications related to stoma closure. Additionally, DS can cause significant mental stress, particularly in Chinese culture, where it can severely impact patients' social functioning[12-14,20]. Therefore, patients with ultralow rectal cancers who can be exempted from stoma need to be screened out to reduce the negative impacts. To our knowledge, this

Table 2 Perioperative outcomes of patients who underwent laparoscopic intersphincteric resection before and after propensity score matching

Variables	Before PSM		*P* value	After PSM		*P* value
	DS (*n* = 421)	SF (*n* = 84)		DS (*n* = 78)	SF (*n* = 78)	
Operative time, median (range) min	172 (90, 335)	171 (85, 485)	0.015	174 (90, 335)	168 (90, 480)	0.109
Blood loss, median (range) mL	50 (20, 800)	50 (5, 500)	0.862	50 (10, 200)	50 (5, 500)	0.611
Conversion to open surgery	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Postoperative complication	58 (13.8)	16 (19.0)	0.212	12 (15.4)	15 (19.2)	0.481
CD grade I-II	43 (10.2)	8 (9.5)	0.516	10 (12.8)	7 (9.0)	0.602
CD grade ≥III	15 (3.6)	8 (9.5)	0.035	2 (2.6)	8 (10.3)	0.050
Anastomotic leakage	32 (7.6)	11 (13.1)	0.099	2 (2.6)	10 (12.8)	0.035
Grade A-B	30 (7.1)	6 (7.1)	0.996	2 (2.6)	5 (6.4)	0.439
Grade C	2 (0.5)	5 (6.0)	< 0.001	0 (0)	5 (6.4)	0.069
Ileus	17 (4.0)	0 (0)	0.123	5 (6.4)	0 (0)	0.069
Hemorrhage postoperation	0 (0)	1 (0)	0.370	0 (0)	1 (1.3)	0.316
Mortality	2 (0.5)	1 (1.2)	0.999	1 (1.3)	1 (1.3)	0.669
Reoperation	6 (1.4)	5 (6.0)	0.074	0 (0)	5 (6.4)	0.069
Postoperative hospital stay (day)	9 (4-51)	11 (4-37)	0.070	10 (5-30)	12 (6-37)	0.275
Anastomosis recurrence	8 (1.9)	0 (0)	0.427	2 (2.6)	0 (0)	0.477
Rectovaginal fistula	4 (1.0)	1 (1.2)	0.363	0 (0)	1 (0)	0.998
Anastomotic stricture	21 (5.0)	0 (0)	0.206	2 (2.6)	0 (0)	0.477
Completion rate of postoperative chemotherapy	191/220 (86.8)	23/39 (59.0)	< 0.001	22/25 (88.0)	20/24 (88.9)	0.933
Permanent stoma	47 (11.2%)	2 (2.3%)	< 0.001	5 (6.4)	2 (2.6)	0.521

Data are presented as *n* (%). CD: Clavien-Dindo; PSM: Propensity score matching; DS: Diverting stoma; SF: Stoma-free.

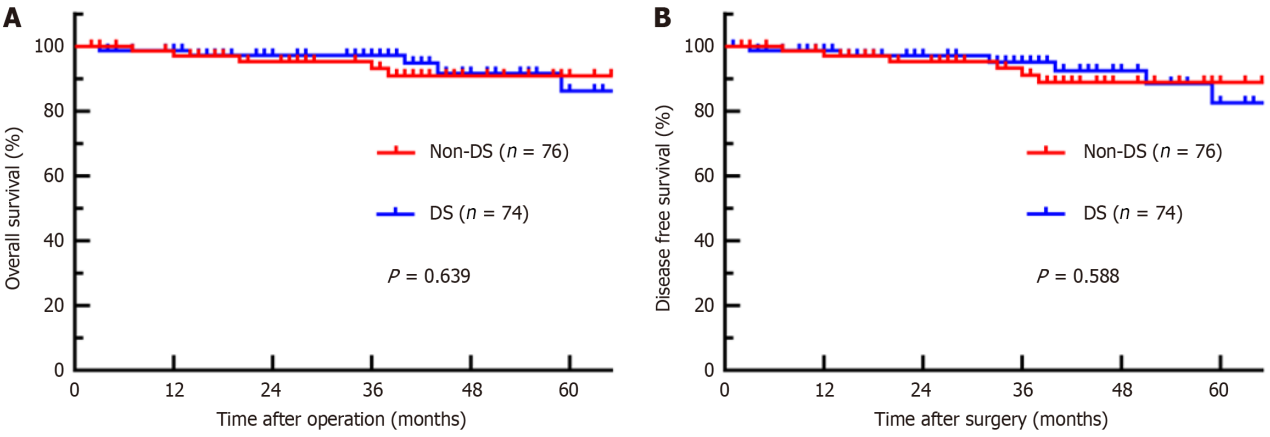

Figure 2 Three-year overall survival and disease-free survival in patients who underwent intersphincteric resection with diverting stoma and without diverting stoma after propensity score matching. A: Overall survival; B: Disease-free survival. DS: Diverting stoma.

study was the first to explore the feasibility of Ls-ISR without stoma using the PSM method. In our study, a multivariate analysis of the baseline cohort revealed that male sex, nCRT, and tumor height from the AV ≤ 4 cm were independent risk factors for AL, whereas LCA retention and DS were protective factors. We proposed and clarified that female patients who did not undergo nCRT and the LCA was preserved intraoperatively had an extremely low risk of AL.

The benefits of stoma are balanced by the risk of leakage and stoma-related complications during rectal resection. Therefore, surgeons should focus not only on the consequences of AL but also on the risk of stoma-related complications. Few studies have examined the use of the Ls-ISR to identify candidates who can avoid stomas, primarily because of the

Table 3 The univariate analysis and multivariate analysis of anastomotic leakage in baseline cohorts and non-diverting stoma cohorts

Variable	Baseline cohort (*n* = 505)				SF cohort (*n* = 84)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Sex (male *vs* female)	2.883 (1.310-6.343)	0.009	2.644 (1.161-6.020)	0.021	2.741 (0.673-11.159)	0.159	2.648 (0.606-11.575)	0.196
Age (≥ 60 years *vs* < 60 years)	0.738 (0.397-1.370)	0.336			0.707 (0.187-2.669)	0.609		
BMI (≥ 25 kg/m^2 *vs* < 25 kg/m^2)	1.899 (1.020-3.536)	0.043	1.716 (0.884-3.330)	0.111	2.450 (0.679-8.841)	0.171	2.678 (0.672-10.678)	0.163
Diabetes (yes *vs* no)	1.544 (0.684-3.485)	0.296			1.580 (0.293-8.509)	0.594		
nCRT (yes *vs* no)	4.805 (2.429-9.502)	< 0.001	6.024 (2.830-12.822)	< 0.001	-	-		
LCA retention (yes *vs* no)	0.068 (0.341-0.102)	0.105	0.417 (0.209-0.830)	0.013	0.393 (0.028-0.891)	0.039	0.312 (0.021-0.802)	0.027
Diverting stoma (yes *vs* no)	0.564 (0.273-1.167)	0.123	0.204 (0.087-0.481)	< 0.001				
Maximal tumor size (> 35 mm *vs* ≤ 35 mm)	0.925 (0.498-1.718)	0.805			1.167 (0.311-4.376)	0.819		
TNM stage (III–IV *vs* I-II)	1.254 (0.667-2.355)	0.482			--	--		
Height of tumor from the anal verge (≤ 4 cm *vs* > 4 cm)	2.563 (0.986-6.658)	0.053	4.160 (1.488-11.634)	0.007	1.587 (0.183-13.780)	0.675		
Vascular invasion (yes *vs* no)	1.433 (0.697-2.947)	0.328			1.253 (0.238-6.594)	0.790		
Nerve invasion (yes *vs* no)	1.563 (0.740-3.303)	0.242			2.741 (0.673-11.159)	0.159	2.648 (0.606-11.575)	0.196

BMI: Body mass index; nCRT: Neoadjuvant chemotherapy; LCA: Left colic artery; SF: Stoma-free; CI: Confidence interval.

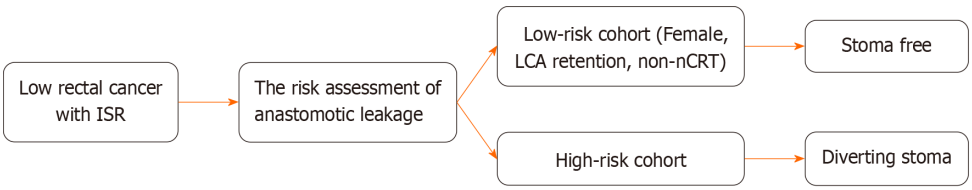

Figure 3 Clinical decision of stoma based on the risk assessment of anastomotic leakage. LCA: Left colic artery; ISR: Intersphincteric resection; nCRT: Neoadjuvant chemoradiotherapy.

high risk of AL and severe complications. A previous meta-analysis of data from four randomized controlled trials revealed a significant reduction in clinically symptomatic leakage (OR = 0.32, 95%CI: 0.17-0.59) and fewer repeat operations (OR = 0.27; 95%CI: 0.14-0.51) in patients with DS. Consequently, the authors recommended the use of stoma after low anterior resection in patients with rectal cancer[2]. Another study demonstrated that the use of a stoma could significantly reduce the incidence of AL (0.8% *vs* 5.1%, *P* = 0.005) after ultralow anterior resection for rectal cancer[21]. In our previous study, we analyzed the risk factors for AL after Ls-ISR. We found that male sex, neoadjuvant therapy, not preserving the LCA, and not performing diverting ileostomy were independent risk factors for AL in patients with ultralow rectal cancer who underwent Ls-ISR[7].

In contrast, other investigators have suggested that the routine use of a stoma is not advisable because their studies revealed no reduction in the incidence of leakage[22]. Many potential problems are associated with stoma creation, including reduced quality of life, stoma-related morbidity[23], financial impact, secondary hospitalizations for stoma closure, and the possibility of permanent stoma[24]. Permanent stoma presents a dilemma. Although a DS can reduce the incidence of AL, it can also lead to a permanent stoma if stoma closure fails. The reasons for this failure are varied and include stoma-related complications, tumor factors (such as local recurrence and metastasis), and patient factors (such as physical tolerance to anesthesia and willingness to undergo reoperation). In our study, sphincter preservation in the DS

Table 4 Clinical characteristics and outcomes between the high-risk and low-risk cohorts of anastomotic leakage patients

Variables	High-risk cohort of AL (*n* = 408)	Low-risk cohort of AL (*n* = 97)	*P* value
Tumor size, median (range) mm			0.212
> 35	208 (60.0)	42 (43.3)	
≤ 35	200 (40.0)	55 (56.7)	
Differentiation status			0.625
Poor	61 (15.0)	12 (12.4)	
Well-moderate	347 (85.0)	85 (87.6)	
pT stage			0.014
0-2	160 (39.2)	52 (53.6)	
3	248 (60.8)	45 (46.4)	
pN stage			0.267
N+	149 (36.5)	29 (29.9)	
N0	259 (63.5)	68 (70.1)	
M stage			0.140
M1	9 (2.2)	0 (0)	
M0	399 (97.8)	97 (100)	
pTNM stage			0.047
I-II	252 (61.8)	71 (73.2)	
III-IV	156 (38.2)	26 (26.8)	
Tumor height from anal verge, median (range) cm			0.530
≤ 4.0	309 (75.7)	77 (79.4)	
> 4.0	99 (24.3)	20 (20.6)	
Operative time, median (range) min	164 (130-195)	175 (139-218)	0.006
Blood loss, median (range) mL	50 (20-50)	50 (20-100)	0.003
Conversion to open surgery	0 (0)	0 (0)	1
Postoperative complication	67 (16.4)	7 (7.2)	0.021
CD grade I-II	46 (11.3)	5 (5.2)	0.072
CD grade ≥ III	21 (5.1)	2 (2.1)	0.299
AL	42 (10.3)	2 (2.1)	0.010
Grade A-B	35 (8.6)	2 (2.1)	0.027
Grade C	7 (1.7)	0 (0)	0.415
Mortality	3 (0.7)	0 (0)	0.397
Reoperation	10 (2.5)	1 (1.0)	0.635
Postoperative hospital stay (day)	9 (4-50)	10 (4-47)	0.081
Anastomosis recurrence	7 (1.7)	1 (1.0)	0.974

Data presented as *n* (%). AL: Anastomotic leakage; CD: Clavien-Dindo.

group failed in 47 patients, with anastomotic factors responsible for 22 patients, tumor factors for 19 patients, and patient-related factors for 6 patients. In the SF group, sphincter preservation failed in 2 patients, both due to anastomotic factors.

Finally, our study revealed no significant difference in long-term survival between patients in the low-risk cohort for AL who avoided a DS and those who underwent the procedure. We attribute this finding to the comparable rates of postoperative AL and other serious complications between the two groups, which allowed for the timely completion of adjuvant therapy. Completing adjuvant therapy on schedule is crucial for reducing tumor recurrence and improving OS and DFS. A nationwide investigation by Gadan *et al*[25], which included 4130 patients with low rectal cancer, revealed

that a DS affected only short-term complications and did not impact OS or DFS.

Our study had several limitations. First, this cohort study was retrospective and was conducted by a single surgical team, which may introduce potential bias. The baseline data tended to include a low AL population, and the overall sample size was small. Although propensity score adjustment may have reduced selection bias, residual or confounding factors may persist. In the multivariate analysis, we included variables based on univariate analysis, clinical experience, and previously reported risk factors; however, selection bias was still difficult to avoid. Second, the number of patients with leakage was small, leading to significant differences in the statistical results. Additionally, the proportion of patients who received nCRT was relatively low in our study, raising questions about whether these conclusions apply to patients who have undergone neoadjuvant therapy.

CONCLUSION

In conclusion, DS could be avoided in female patients without nCRT by preserving the LCA without compromising AL risk or oncological outcomes.

FOOTNOTES

Author contributions: Hu G and Ma J contributed to data acquisition, data analysis and follow-up, and drafting the manuscript; Qiu WL contributed to data analysis and follow-up and drafting the manuscript; Mei SW and Zhuang M contributed to data acquisition; Xue J and Liu JG provided critical revision of the manuscript; Tang JQ contributed to research design and critical revision of manuscript; All authors contributed to the conception and design of the study. Hu G and Qiu WL contributed equally to this work as co-first authors.

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ORIGINAL ARTICLE

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Effects of postoperative quantitative assessment strategy-based nursing in patients with colorectal cancer

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Abstract

BACKGROUND

Scientifically sound and reasonable care strategies in surgical nursing play a crucial role in facilitating postoperative recovery and preventing complications. This study focused on the application of quantitative assessment strategies to postoperative care. By quantitatively analyzing the effects of nursing interventions, we explored their feasibility and effectiveness at improving postoperative recovery quality and reducing the incidence of complications. This study provides a scientific basis for nursing practice and offers new insights into nursing management with significant clinical value.

AIM

To analyze the efficacy of postoperative quantitative assessment strategy-based nursing care for patients with colorectal cancer (CRC).

METHODS

This randomized controlled trial evaluated the ability of nursing interventions using a quantitative assessment strategy to prevent postoperative complications and enhance patient recovery. Patients with CRC were randomly divided into routine nursing (RN) and quantitative assessment strategy nursing (QASN) groups. The RN group received standard care, while the QASN group also underwent screenings for visual analog scale for pain, Barthel Index for functional recovery, and self-rating anxiety scale and self-rating depression scale for psychological status. Follow-ups were conducted on postoperative days 1, 7, 14, 28, and 56.

RESULTS

The participants' baseline characteristics did not significantly differ between study groups, thereby ensuring the reliability of the results. The QASN *vs* RN group showed significant improvements in pain management (visual analog scale scores) and psychological status (self-rating anxiety scale and self-rating depre-

ssion scale scores) and a reduced incidence of postoperative complications ($P < 0.05$). The follow-up evaluations at specified intervals confirmed these findings, indicating that quantitative assessment strategies significantly enhanced patients' postoperative pain management and psychological well-being.

CONCLUSION

Nursing interventions using structured quantitative assessments demonstrated significantly improved postoperative recovery and quality of life in patients with CRC, supporting their integration into standard postoperative care protocols.

Key Words: Postoperative; Colorectal cancer; Quantitative assessment strategy-based nursing; Patient recovery; Pain management; Nursing evaluation

Core Tip: In this study, we developed individualized interventions based on the patients' actual conditions. By quantitatively assessing the patient's overall condition, dynamic adjustments were made based on the patient's change in condition, pain level, and postoperative complications. The study demonstrated that care based on quantitative assessment strategies significantly reduces postoperative complications and improves recovery in patients with colorectal cancer, and the findings support the benefits of combining care plans based on quantitative assessment strategies with standard postoperative care protocols.

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INTRODUCTION

Colorectal cancer (CRC), including cancer of the colon and rectum, is a common malignant tumor of the digestive tract. Owing to unhealthy eating habits and lifestyles, the incidence and mortality rates are increasing annually. In 2020, CRC was the third most common cancer worldwide, with approximately 1.93 million new cases[1]. According to a 2022 report from the National Cancer Center of China, CRC ranked second in the number of new cases of malignant tumors and fourth in mortality in China from 2016 to 2022[2]. The pathophysiological mechanisms of CRC involve multiple factors and complex signaling pathways. The main mechanisms include defects in DNA repair pathways, such as mutations in mismatch repair genes or epigenetic silencing, leading to microsatellite instability. Stromal cells in tumor tissues exhibit immunosuppressive and pro-tumorigenic features that upregulate the transforming growth factor-β and wingless-related integration site signaling pathways, network signals that control cell proliferation, survival, differentiation, and apoptosis. Oxidative stress–induced DNA damage is an important factor in the development of CRC.

CRC can be treated using various methods, including surgery, radiotherapy, chemotherapy, and immunotherapy. Comprehensive treatment based on surgical resection is the mainstay of CRC treatment, and the specific surgical method used depends on tumor location, size, and stage as well as overall patient health. However, surgery can negatively impact the patient's mind and body, leading to reduced quality of life. Pain and postoperative complications, such as adhesions, small bowel obstruction, thrombosis, infections, and anastomotic leakage, can further deteriorate patient health[3,4]. High-quality nursing care is crucial during the postoperative recovery phase in patients with CRC. Effective nursing interventions can reduce postoperative complications, promote recovery, improve therapeutic effects, and improve health-related quality of life[5,6]. Traditional postoperative nursing practices often lack a structured and systematic approach to comprehensively monitoring and evaluating patient rehabilitation, necessitating innovative strategies and quantitative tools to analyze nursing care quality and effectiveness.

Recent advancements in nursing research have highlighted the benefits of integrating quantitative assessment strategies into postoperative care, showing significant potential for enhancing nursing quality. By adopting a system- and data-driven approach, quantitative evaluations in nursing care can objectively and comprehensively assess patient progress, facilitating better clinical decision-making and personalized care plans. Research indicates that these strategies can improve patient monitoring accuracy, enable the early detection of complications, and support the use of evidence-based nursing interventions[7,8]. However, comprehensive research exploring the full potential of these strategies in the postoperative care of patients with CRC is lacking. This study aimed to address this knowledge gap by analyzing the effects of postoperative nursing care based on quantitative assessment strategies in patients with CRC. This study's innovation lies in its systematic approach to evaluating the impact of structured assessment strategies on patient outcomes. By providing empirical evidence of the benefits of these strategies, this study sought to determine the need to incorporate quantitative assessments into standard nursing care practices for cancer patients.

MATERIALS AND METHODS

Patient selection

One hundred and forty postoperative patients with CRC admitted to our hospital between January 2022 and June 2023 were included. Patients were randomly assigned to the routine nursing (RN) group (n = 72) and the quantitative assessment strategy nursing (QASN) group (n = 68). The RN group received standardized routine postoperative care including nutritional guidance and health education. The QASN group received routine care in addition to the following specialized nursing interventions: (1) Assessments of each patient's condition and postoperative recovery needs; (2) Regular quantitative comprehensive evaluations administered once weekly to assess postoperative complications, pain, functional recovery, and psychological status; (3) Dynamic adjustment of nursing measures in which nursing plans were adjusted in real time based on the evaluation results to ensure their relevance and efficacy; and (4) Nursing team collaboration, the primary members of which included specialized nurses and registered nurses and secondary members included rehabilitation therapists and psychological counselors. The team worked together to ensure care continuity and comprehensiveness. This study was approved by the hospital ethics committee.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) CRC confirmed by imaging and pathological biopsy; (2) Treatment with laparoscopic radical resection in our hospital; (3) Age 18-75 years; (4) No hematologic–immune system disorders; (5) No drug allergies; and (6) Voluntary participation and ability to provide written informed consent.

The exclusion criteria were as follows: (1) Comorbid other tumors or heart failure; (2) Severe organic lesions of the heart, liver, kidney, spleen, or lungs; (3) Cognitive or psychiatric disorders or inability to communicate normally, including memory disorders, aphasia, agnosia, dysarthria, dyspraxia, and visuospatial disorders; (4) Currently pregnant or breastfeeding; (5) Family or personal history of psychiatric disorders; and (6) Poor study adherence, early study withdrawal, or transfer to another hospital.

Study design

This randomized controlled trial evaluated the effectiveness of postoperative nursing care based on a quantitative assessment strategy for patients with CRC. Patients were followed up immediately after surgery, and assessments were performed on postoperative days 1, 7, 14, 28, and 56. The effectiveness of the quantitative assessment strategy was determined by the intergroup comparison of postoperative complications, functional recovery, pain levels, and psychological status (Table 1)[9-11].

Statistical analysis

All data were collected using an electronic case system through standardized questionnaires that included basic patient information, medical history, postoperative recovery, occurrence of complications, psychological status, and quality of life. Trained professionals conducted data entry to ensure accuracy and completeness. SPSS statistical software (version 25.0) was used for the data analysis. Measurement data are expressed as mean ± SD and were compared between groups using independent sample t-tests. Categorical data are expressed as number of cases (percentage) and were compared between groups using the χ^2 test or Fisher's exact test. All statistical analyses were two-sided, with values of $P < 0.05$ considered statistically significant. A biomedical statistician performed all of the statistical analyses.

RESULTS

Between January 2022 and June 2023, 147 postoperative patients with CRC were evaluated for eligibility. Seven patients were excluded, including four with severe cardiovascular, hepatic, or renal comorbidities; one who died before surgery; and two who were lost to follow-up. The remaining 140 patients were randomly assigned to the QASN (n = 68) or RN (n = 72) group. No perioperative deaths occurred in either group during the follow-up period (56 days). No significant intergroup differences were found in the baseline or surgical characteristics (Table 2).

Postoperative complications

Postoperative complications of CRC can significantly affect a patient's physical and psychological recovery, length of hospitalization, and overall prognosis. We compared the incidence of postoperative complications between the QASN and RN groups (Table 3). The complications analyzed included wound infection, pulmonary infection, intestinal obstruction, anastomotic leakage, urinary retention, urinary tract infection, postoperative bleeding, deep vein thrombosis, and malnutrition. Complications that did not occur were excluded from the statistical analysis. Five (7.35%) and 14 (19.44%) complications occurred in the QASN and RN groups, respectively. One patient in the RN group developed pulmonary infections and surgical site infections. Fisher's exact test showed that the overall complication rate was significantly lower in the QASN *vs* RN group ($P < 0.05$).

Functional recovery and pain relief

Pain is often accompanied by discomfort and distressing emotions, which can drain a patient's energy and reduce their recovery motivation. Pain can also limit a patient's mobility, leading to functional impairment and muscle atrophy.

Table 1 Nursing interventions based on quantitative evaluation strategies

Item	Specific operation
Pain assessment	VAS[9]
Functional recovery assessment	Barthel index[10]
Psychological state assessment	SAS; SDS[11]
Complications assessment	Record the occurrence and severity of postoperative complications

VAS: Visual analog scale; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

Table 2 Comparison of general characteristics of the patients, *n* (%)

Characteristic	QASN group (*n* = 68)	RN group (*n* = 72)	*P* value
Age (year), mean ± SD	60.10 ± 9.60	59.67 ± 8.89	0.947
BMI (kg/m²), mean ± SD	24.75 ± 3.94	25.50 ± 3.69	0.777
Gender	-	-	0.247
Male	35 (51.9)	29 (40.0)	-
Female	33 (48.1)	43 (60.0)	-
Disease type	-	-	0.518
Colon cancer	35 (51.9)	42 (57.8)	-
Rectal cancer	33 (48.1)	30 (42.2)	-
TNM staging	-	-	0.319
Phase I	25 (36.5)	18 (24.4)	-
Phase II	22 (32.7)	27 (37.8)	-
Phase III	21 (30.8)	27 (37.8)	-
Educational level	-	-	0.507
College degree or above	33 (48.5)	29 (40.0)	-
High school/vocational	22 (32.3)	24 (33.3)	-
Junior high school or below	13 (19.2)	19 (26.7)	-
Complications	-	-	0.471
Hypertension	21 (30.8)	29 (40.0)	-
Type 2 diabetes	25 (36.5)	21 (28.9)	-
Lacunar cerebral infarction	16 (23.1)	16 (22.2)	-
Hypothyroidism	6 (9.6)	6 (8.9)	-
Dukes stage	-	-	0.867
A	17 (25.0)	14 (20.0)	-
B	27 (40.4)	29 (40.0)	-
C	16 (23.1)	19 (26.7)	-
D	8 (11.5)	10 (13.3)	-

QASN: Quantitative assessment strategy nursing; RN: Routine nursing; BMI: Body mass index; TNM: Tumor node metastasis.

Relevant data were collected to compare functional recovery and pain relief at different pre- and postoperative time points (Table 4). Preoperatively, no significant intergroup differences were found between the QASN and RN groups in Barthel index (68 ± 10 *vs* 68 ± 9) and visual analog scale (VAS) score (3.1 ± 1 *vs* 3.0 ± 0.8), respectively ($P > 0.05$). On postoperative day 1, a significant decrease in Barthel index (40 ± 7 in both groups) and increase in VAS scores (6.8 ± 1 *vs* 7.0 ± 1.1 in QASN and RN group, respectively). On postoperative day 7, the mean Barthel index was significantly higher

Table 3 Comparison of postoperative complication rates between the two groups, *n* (%)

Complication	QASN group (*n* = 68)	RN group (*n* = 72)	*P* value
Incision infection	2 (2.94)	3 (4.17)	-
Pulmonary infection	0 (0.00)	2 (2.78)	-
Intestinal obstruction	1 (1.47)	1 (1.39)	-
Anastomotic fistula	1 (1.47)	1 (1.39)	-
Uroschesis	0 (0.00)	2 (2.78)	-
Urinary tract infection	1 (1.47)	1 (1.39)	-
Postoperative bleeding	0 (0.00)	1(1.39)	-
Deep vein thrombosis	0 (0.00)	1 (1.39)	-
Malnutrition	0 (0.00)	2 (2.78)	-
Total	5 (7.35)	14 (19.44)	0.041

QASN: Quantitative assessment strategy nursing; RN: Routine nursing.

Table 4 Comparison of functional recovery and pain level between the two groups of patients, mean ± SD

Item	Classification	Preoperative	Postoperative				
			1 day	7 days	14 days	28 days	56 days
BI	QASN group (*n* = 68)	68 ± 10	40 ± 7	52 ± 8	61 ± 10	75 ± 12	80 ± 13
	RN group (*n* = 72)	68 ± 9	40 ± 8	45 ± 9	52 ± 9	65 ± 10	70 ± 11
	P value	0.999	0.999	0.371	0.039	0.013	0.009
VAS	QASN group (*n* = 68)	3.1 ± 1	6.8 ± 1	5.7 ± 0.8	4.5 ± 0.8	3.5 ± 0.7	2.5 ± 0.5
	RN group (*n* = 72)	3.0 ± 0.8	7.0 ± 1.1	5.8 ± 1	5.5 ± 0.9	5.0 ± 0.8	4.5 ± 0.7
	P value	0.899	0.827	0.899	0.015	0.007	0.001

BI: Barthel Index; VAS: Visual analog scale; QASN: Quantitative assessment strategy nursing; RN: Routine nursing.

in the QASN group (52 ± 8 *vs* 45 ± 9, $P < 0.05$), while the mean VAS score was lower (5.7 ± 0.8 *vs* 5.8 ± 1, $P > 0.05$). The differences increased on postoperative days 14, 28, and 56, with the QASN group showing higher Barthel indices and lower VAS scores at each time point (all $P < 0.05$). These results showed that pain management in the QASN group minimized pain, reduced postoperative complications, facilitated early mobility and functional recovery, shortened the length of hospital stay, reduced medical costs, and improved patient satisfaction.

Psychological status

The effectiveness of the nursing intervention was further confirmed by the postoperative self-rating anxiety scale (SAS) and self-rating depression scale (SDS) scores (Table 5). The preoperative SAS and SDS scores did not significantly differ between groups ($P > 0.05$), indicating comparable preoperative anxiety and depression. However, on postoperative day 56, the SAS and SDS scores were significantly lower in the QASN *vs* RN group ($P < 0.05$). These findings suggest that the patients' anxiety and depression status improved significantly more in the QASN *vs* RN group.

DISCUSSION

Nursing care based on quantitative assessment strategies involves systematic numerical measurements and analyses that evaluate patient care quality and outcomes. This study demonstrated that the implementation of a quantitative assessment-based nursing intervention significantly improved postoperative outcomes in patients with CRC. Continuous follow-up provided in this study during the patients' postoperative recovery allowed for the timely modification and optimization of the nursing care plan, thereby enhancing both outcomes and patient satisfaction. Patients in the QASN group showed lower complication rates, better pain management, improved functional recovery, enhanced mental health, and a higher quality of life than those in the RN group.

Table 5 Comparison of postoperative psychological assessment between the two groups

Classification	Item	Preoperative	Postoperative
QASN Group (*n* = 68)	SAS	55.3 ± 10.2	34.2 ± 7.5
RN Group (*n* = 72)		54.7 ± 9.8	42.6 ± 8.1
P value		0.945	0.021
QASN Group (*n* = 68)	SDS	60.1 ± 11.5	38.1 ± 8.4
RN Group (*n* = 72)		59.4 ± 10.9	45.3 ± 8.9
P value		0.938	0.019

QASN: Quantitative assessment strategy nursing; SAS: Self-rating anxiety scale; RN: Routine nursing; SDS: Self-rating depression scale.

There is an increasing trend toward younger patients with CRC, and it remains more prevalent in elderly patients. Studies have shown that the incidence and severity of comorbidities directly affect patient prognosis and survival rates [12]. The involvement of professional nursing care teams including doctors, specialized nurses, and rehabilitation professionals significantly improves patient prognosis and reduces early postoperative mortality rates[13]. Our findings also indicated that nursing interventions using quantitative evaluation strategies can reduce the incidence of postoperative complications in patients with CRC. The data showed that patients in the QASN group experienced fewer postoperative complications than those in the RN group. Specifically, the incidence of complications such as wound infection, pulmonary infection, and postoperative bleeding was lower in the QASN group, highlighting the potential benefits of implementing quantitative assessment strategies in postoperative care. This improvement may be attributed to strengthened monitoring and early interventions for postoperative complications as well as personalized care plans that include early mobilization, respiratory exercises, efficient nutrition programs, and physical intensity exercises.

Therefore, effective pain management is crucial to a patient's postoperative recovery[14]. Here we assessed the VAS scores of the patients at various postoperative follow-up time points. If a patient's pain score consistently remains high, adjustments to the painkiller type and dosage as well as the addition of non-pharmacological pain management measures (such as cold compresses, hot compresses, and physical therapy) can be considered. Our findings indicate that the use of standardized pain assessment protocols in the QASN group can more effectively control pain, underscoring the role of quantitative assessments in optimizing pain management strategies.

The postoperative psychological state of patients with CRC is a significant factor affecting their postoperative rehabilitation and quality of life[15]. Scientific and reasonable nursing interventions can markedly improve patients' psychological states and enhance postoperative rehabilitation outcomes[16]. The results showed that the SAS and SDS scores were significantly lower in the QASN *vs* RN group ($P < 0.05$). This suggests that the nursing intervention of the QASN group effectively alleviated the patients' anxiety and depression by providing more targeted nursing measures and psychological intervention techniques, such as relaxation training and psychological counseling[17]. In addition, the nurses in the QASN group were trained to have higher psychological care skills and able to provide higher-quality psychological care and social support to improve patients' psychological status[18].

In previous studies, the concept of nursing interventions was vague, assessment process subjective and arbitrary, and operation weak; therefore, it was impossible to provide graded care for each patient's overall condition[19,20]. In this study, we developed personalized interventions based on patients' actual conditions. By quantitatively assessing the patients' overall conditions and grading their nursing risks, we formulated more targeted and graded nursing interventions that were dynamically adjusted according to their changing conditions, pain level, and postoperative complications to promote their early mobility and functional recovery. The use of mathematical methods to quantify the results of evaluation components has high objectivity and reliability, which supports the incorporation of quantitative assessment strategies by standard postoperative care providers. However, the single-center design and relatively small sample size limited the generalizability of our findings. Additionally, the choice of quantitative assessment tools may have affected our results. Larger multicenter studies are needed to validate our findings and explore the long-term impact of such interventions.

CONCLUSION

Nursing interventions based on structured quantitative assessments have significantly improved the postoperative recovery and quality of life of patients with CRC. These findings support the use of these strategies in routine clinical practice to enhance patient care quality and outcomes.

FOOTNOTES

Author contributions: Tan XQ drafted the manuscript and gave final approval of the version to be published; Huang XL designed this

study, collected and analyzed the data; Tan XQ and Huang XL took part in this study as endoscopic operators or assistants; and all authors thoroughly reviewed and endorsed the final manuscript.

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SYSTEMATIC REVIEWS

Systematic review and meta-analysis comparing extraperitoneal and transperitoneal routes of colostomy-related complications

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Abstract

BACKGROUND

Complications associated with stomas—including parastomal hernia (PSH), prolapse, mucocutaneous separation, and stoma retraction—provide considerable postoperative challenges for colostomy patients. Selecting between extraperitoneal colostomy (EPC) and transperitoneal colostomy (TPC) pathways is therefore essential for mitigating these complications.

AIM

To analyze the existing data regarding the efficacy of EPC compared to TPC in reducing stoma-related complications post-colostomy.

METHODS

PubMed, Google Scholar, EMBASE, MEDLINE, and the Cochrane Library were adopted to uncover pertinent papers in which EPC and TPC approaches were compared. We then conducted a meta-analysis using RevMan 5.4.1.

RESULTS

Both laparoscopic (Lap) and open approaches showed a reduced incidence of PSH

in EPC relative to TPC (P < 0.00001 and P = 0.02 respectively). In addition, Lap EPC depicted a lesser incidence of prolapse, mucocutaneous separation, and stoma retraction (P = 0.007, P = 0.03, and P = 0.01, respectively) compared to Lap TPC. However, EPC and TPC did not differ with respect to operation time, blood loss, edema, ischemia, necrosis, or infection after the LAP approach.

CONCLUSION

The extraperitoneal approach may provide benefits in minimizing some stoma-related problems such as PSH, prolapse, mucocutaneous separation, and stoma retraction after colostomy surgery.

Key Words: Colostomy; Extraperitoneal; Transperitoneal; Parastomal hernia; Abdominoperineal resection

Core Tip: The study provides an inclusive meta-analysis comparing extraperitoneal (EPC) and transperitoneal (TPC) routes in colostomy surgery, emphasizing significant reductions in parastomal hernia, prolapse, stoma retraction, and mucocutaneous separation with the EPC approach. Despite previous studies suggesting benefits, newer evidence from 1973 patients highlights methodological improvements and the inclusion of previously overlooked cohort studies. Findings indicate comparable operative outcomes between EPC and TPC routes, challenging previous assertions. The study underscores EPC's potential to enhance postoperative quality of life by minimizing specific complications.

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INTRODUCTION

Colorectal cancer constitutes approximately 10% of newly diagnosed malignancies and cancer-related fatalities globally each year, and ranks as the third most prevalent cancer in men and the second most prevalent in women worldwide[1,2]. Conventional surgical techniques, including abdominoperineal resection (APR) and sigmoidectomy, are regarded as safe and effective interventions for these individuals[3,4]. However, even with the progress in surgical instrumentation and methodologies, some patients with low rectal cancer still require sigmoidostomy, which entails a significant risk of complications[4-6].

A colostomy requires creating a hole in the large intestine by pulling the healthy segment through an incision in the abdominal wall, thus establishing an alternate route for waste excretion[7]. This aperture, along with the connected stoma, offers an additional route for waste expulsion from the body[8], and a permanent stoma is conventionally established *via* a transperitoneal colostomy (TPC). In 1958, Goligher created an extraperitoneal colostomy (EPC) methodology, which has subsequently gained widespread acceptance. This approach conserves lateral space reduces the possibility of blockage and provides enhanced coverage *via* a lateral peritoneal flap.

Regarding the prolonged use of these techniques, a consensus on the efficacy of permanent sigmoidostomy in avoiding parastomal hernia (PSH) remains unclear. The European Hernia Society contends that there are inadequate data to demonstrate the advantage of EPC over TPC in decreasing the incidence of PSH[7]. However, prior meta-analyses of open surgical techniques indicate that colostomies formed by the EPC route show a reduced incidence of PSH relative to those constructed *via* the TPC route[9]. Although studies on laparoscopic APR have revealed that the laparoscopic EPC approach reduces the rate of PSH[10], performing an EPC colostomy during laparoscopic APR is more challenging due to the technical complexities[11]. Deciding whether to pursue an open or laparoscopic extraperitoneal or transperitoneal route for a permanent stoma placement remains a point of perplexity for many surgeons. It is thus crucial to carefully consider the feasibility of each approach based on the specific patient's condition, anatomy, and potential risks and benefits associated with the procedure. We herein assessed the impact of open and laparoscopic EPC *vs* TPC routes on colostomy-related complications.

MATERIALS AND METHODS

In this meta-analysis we evaluated the EPC and TPC approaches using randomized controlled trials (RCTs) and retrospective studies (RS). Our analysis was executed in accordance with the Recommended Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards[12]. Ethical authorization and patient consent were unnecessary, since the analysis used previously published research.

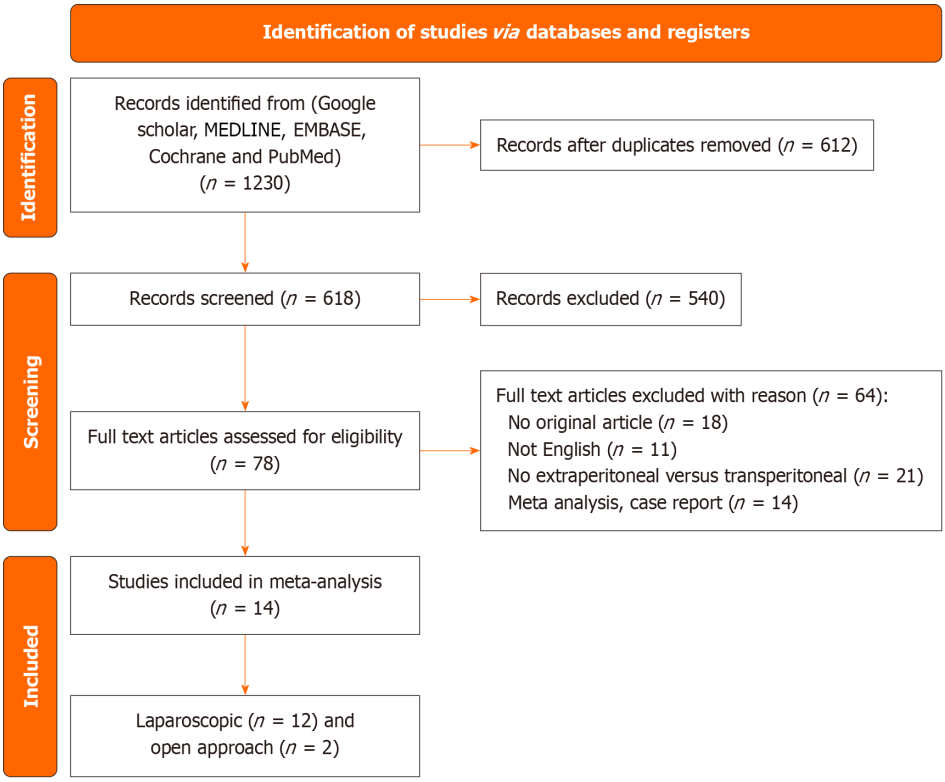

Figure 1 Literature screening process.

Search strategy

We conducted an extensive search of the PubMed, MEDLINE, Google Scholar, Cochrane Library, and Web of Science databases for publications published between 1976 and 2024. This investigation focused on research that compared the EPC and TPC approaches for individuals having an end colostomy due to cancer or other ailments. A search was implemented using the following key terms: Extraperitoneal; abdominoperineal resection; transperitoneal; colostomy; and PSH. Two separate evaluators assessed the selected studies by reviewing their entire texts (Figure 1 illustrates the outcomes of the search approach).

Inclusion criteria

The following criteria were considered for inclusion.

Participants: Adult patients undergoing colonic surgery that comprised either an end colostomy or APR.

Interventions: EPC and TPC.

Comparison: EPC *vs* TPC.

Outcomes: PSH, prolapse, necrosis, infections, retraction, ischemia, and mucocutaneous separation.

Exclusion criteria

The following criteria were considered for exclusion. Studies that lacked specifically targeted data. Incomplete papers. Case reports and meta-analyses. Non-English language papers

Data acquisition

Two reviewers individually assessed the search results, and all concerns regarding inclusiveness were addressed *via* dialogue. Publications were included using standardized forms that recorded data from studies, including study design, EPC or TPC colostomy, author, country, year of publication, surgical method (whether open or laparoscopic), period of follow-up, and patient number as outlined in Table 1.

Postoperative outcomes—including operation time and blood loss—were included. Additionally, problems associated with colostomy (such as PSH, prolapse, edema, mucocutaneous separation, infection, necrosis, ischemia, and stoma retraction) were documented as shown in Table 2.

Statistical analysis

We conducted our analysis using Review Manager (RevMan) version 5.4.1, applying the Mantel-Haenszel method for statistical evaluation. Both dichotomous and continuous data were assessed to calculate odds ratios (ORs) with 95%CI,

Table 1 Characteristics of included studies, median (25th-75th percentiles)

Ref.	Country	Year	Approach (open/lap)	Study design	Group EPC/TPC	Number of patients EPC/TPC	Follow-up month
Heiying *et al*[13]	China	2014	Lap	RCTs	EPC/TPC	18/18	17 (12-24)
Whittaker *et al*[14]	England	1976	Open	RS	EPC/TPC	89/162	-
Madoka *et al*[15]	Japan	2012	Lap	RS	EPC/TPC	22/15	23/14
Leroy *et al*[16]	Taiwan	2012	Lap	RS	EPC/TPC	12/10	22.25/36.3
Hino *et al*[17]	Japan	2017	Lap	RS	EPC/TPC	30/29	21 (2-95)
Xiao *et al*[18]	China	2023	Both	RS	EPC/TPC	103/202	17-46
Zhang *et al*[19]	China	2024	Lap	RS	EPC/TPC	37/37	36
Ota *et al*[20]	Japan	2022	Lap	RS	EPC/TPC	105/222	38.0/45.5
Xiao *et al*[21]	China	2022	Lap	RS	EPC/TPC	83/50	6
Wang *et al*[22]	China	2018	Lap	RS	EPC/TPC	108/123	24
Yao *et al*[23]	China	2023	Lap	RS	EPC/TPC	30/30	6
Wang *et al*[24]	China	2024	Lap	RS	EPC/TPC	37/46	32/28
Dong *et al*[25]	China	2012	Lap	RCTs	EPC/TPC	66/62	6-60
Marks *et al*[26]	United States	2005	Open	RS	EPC/TPC	37/190	60

Lap: Laparoscopic; RCTs: Randomized controlled trials; EPC: Extraperitoneal colostomy; TPC: Transperitoneal colostomy.

which provided insights into the statistical differences between the outcomes of EPC and TPC colostomies. Our findings are presented through forest plots. Statistical heterogeneity was evaluated using the I^2 statistic, with heterogeneity categorized as follows: 0%–30% (low), 30%–60% (moderate), 50%–90% (substantial), and 75%–100% (considerable). A significance threshold of $P < 0.05$ was employed for all models.

RESULTS

Our initial search identified 1230 articles, with 612 remaining after duplicate removal. Following the screening process, 78 articles were selected for full-text review. Of these, 14 studies met the inclusion criteria and were included in the final analysis: 12 focused on laparoscopic procedures, and 2 examined open procedures, as shown in Figure 1.

Characteristics of included studies

The included studies consisted of two RCT and 12 RS that involved a total of 1973 patients. Of these, 1495 patients underwent laparoscopic procedures (651 with EPC and 844 with TPC), and 478 patients underwent open procedures (126 with EPC and 352 with TPC).

The studies represented a geographically diverse sample, including data from Asia, Europe, and the United States; and offered a comprehensive perspective on the topic (detailed characteristics of the included studies are summarized in Table 1).

Laparoscopic outcome after EPC vs TPC approaches

Several studies[13-25] collectively encompassed 1362 patients, comprising 568 patients in the EPC and 794 patients in the TPC groups. The analysis of operation time, as depicted in Figure 2A, indicated no statistically significant difference between the two groups. The mean difference was −4.02 (95%CI: −9.51-1.47), with an I^2 of 93% and $P = 0.15$.

Six studies[15,17,18,20,22,24] collectively comprised 1042 patients, with 405 patients in the EPC group and 637 patients in the TPC group. The analysis of blood loss, as depicted in Figure 2B, indicated no statistically significant difference between the two groups. The mean difference was −3.00 (95%CI: −16.10–10.10), with an I^2 of 0% and $P = 0.65$.

Twelve studies[13,15-25] collectively included 1495 patients, with 651 in the EPC group and 844 in the TPC group. Analysis of PSH rates (shown in Figure 3A) revealed a statistically significant difference favoring the EPC group. The PSH rate was 4.3% in the EPC group (28 of 651 patients) compared to 16.4% in the TPC group (139 of 844 patients). The OR was 0.24 (95%CI: 0.16–0.37), with an I^2 of 35% and $P < 0.00001$.

Nine studies[13,16-19,22-25] were collectively composed of 998 patients, with 441 in the EPC group and 557 in the TPC group. As illustrated in Figure 4A, the analysis of prolapse rates revealed a statistically significant difference that favored the EPC group. The prolapse rate was 1.8% in the EPC group (eight of 441 patients) compared to 5.9% in the TPC group

Table 2 Outcomes of included studies, mean ± SD

Ref.	Operation time	Blood loss	Edema	Necrosis	Ischemia	Stoma retraction	Infection	Prolapse	Mucocutaneous separation	Parastomal hernia
EPC/TPC Lap										
Heiying *et al*[13]	14.7 ± 6.4/25.3 ± 8.5	-	0/6	-	1/1	0/0	-	1/0	-	2/0
Whittaker *et al*[14]	361 ± 64/308 ± 80	182 ± 118/203 ± 254	-	2/0	-	-	4/1	-	2/6	1/5
Madoka *et al*[15]										
Leroy *et al* [16]	320.83 ± 65.84/350 ± 64.8	-		0/2	-	-	0/1	0/0	-	0/4
Hino *et al* [17]	291 ± 120/ 306 ± 102.25	43 ± 172.5/66 ± 203.25	-	-	0/2	0/3	1/0	1/4	0/1	4/12
Xiao *et al* [18]	209.47 ± 24.23/ 210.00 ± 24.42	90.67 ± 116.42/ 84.43 ± 41.92	-	-	-	-	3/7	6/10	0/2	7/31
Zhang *et al* [19]	205± 10.75 /205± 12.5	-	-	0/0	-	0/0	-	0/3	-	6/5
Ota *et al*[20]	289± 156.75/345.5± 192.5	50± 143.75/60 ± 407.5	-	-	-	-	17/46	-	-	2/38
Xiao *et al* [21]	23.1± 6/21.4 ± 4	-	-	-	-	-	-	-	-	0/4
Wang *et al* [22]	168.0 ± 21.2/ 170.2 ± 21.2	167.1 ± 73.7/179.1 ± 76.3	10/5	1/2	-	0/6	1/3	0/6	-	5/22
Yao *et al*[23]	26.64 ± 2.45/24.86 ± 2.78	-	-	-	-	1/1	-	0/2	-	0/4
Wang *et al* [24]	155.8 ± 38.2/158.5 ± 32.4	119.4 ± 81.3/108.7 ± 74.7	13/7	-	0/1	2/4	-	0/6	-	1/9
Dong *et al* [25]	21.3 ± 3.5/30.4 ± 4.2	-	-	1/1	-	1/3	-	0/2	-	0/5
EPC/TPC open										
Marks and Ritchie *et al* [26]	-	-	-		-	-	-	-	-	1/22
Whittaker *et al*[14]	-	-	9/16	-	-	-	11/23	2/10	7/17	8/28

EPC: Extraperitoneal colostomy; TPC: Transperitoneal colostomy.

(33 of 557 patients). The calculated OR was 0.39 (95%CI: 0.20–0.77), with an I^2 value of 25% (indicating low heterogeneity), and a significance level of $P = 0.007$.

In three studies[15,17,18] that totaled 401 patients (155 in the EPC and 246 in the TPC groups), we analyzed the rate of mucocutaneous separation; and as shown in Figure 4B, there was a statistically significant difference in favor of the EPC group. The mucocutaneous separation rate was 1.3% (two of 155) in the EPC group compared to 3.6% (nine of 246) in the TPC group. The OR was 0.21 (95%CI: 0.05–0.84), with an I^2 of 0% and $P = 0.03$.

Six studies[15-18,20,22] collectively included 981 patients, with 380 in the EPC and 601 in the TPC groups; and our analysis of infection rates (shown in Figure 5A) did not reveal any difference between the groups. The infection rate was 6.8% (26/380) for EPC and 9.6% (58/601) for TPC, with an OR of 0.79 (95%CI: 0.48–1.32), I^2 of 0%, and $P = 0.38$.

Three studies[13,22,24] consisted of 350 patients, 163 in the EPC and 187 in the TPC groups, and when we analyzed these for edema rates, we uncovered no difference between the groups (Figure 5B). The EPC group possessed an edema

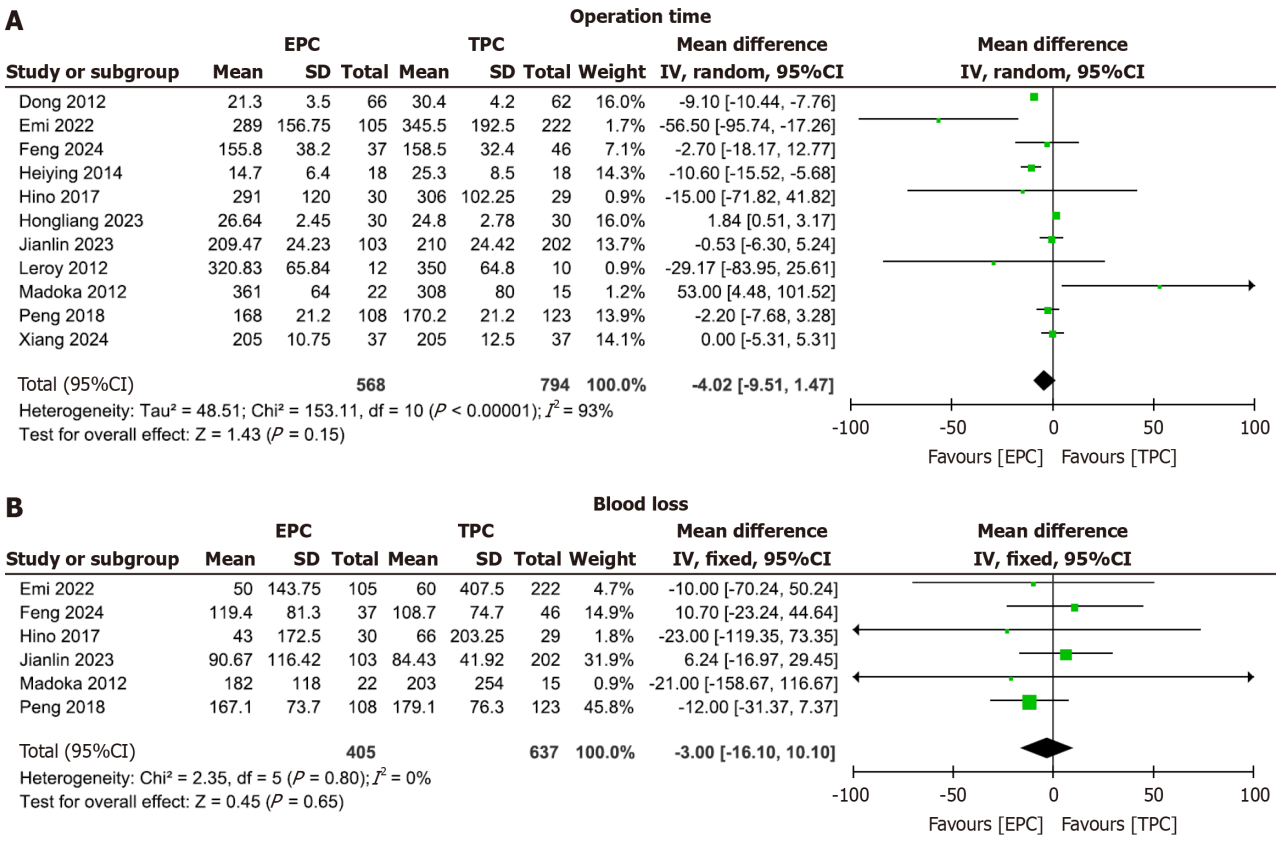

Figure 2 Forest plot of operation time and blood loss. A: Operation time; B: Blood loss after laparoscopic approach. EPC: Extraperitoneal colostomy; TPC: Transperitoneal colostomy.

rate of 14.1% (23 of 163) *vs* 9.6% in the TPC group (18 of 187), for an OR of 1.31 (95%CI: 0.26–6.44), with an I^2 of 72% and P = 0.74.

Seven studies[13,17,19,22-25] entailed 671 patients, with 326 in the EPC group and 345 in the TPC group. As shown in Figure 3B, analysis of stoma retraction showed a statistically significant difference that favored the EPC group. The stoma retraction rate was 1.2% (4 of 326 patients) in the EPC group, compared to 4.9% (17 of 345) in the TPC group, for an OR of 0.29 (95%CI: 0.10–0.78), an I^2 of 0%, and P = 0.01.

When we analyzed five studies of 492 patients for necrosis[15,16,19,22,25] (245 in the EPC group and 247 in the TPC group), we found no difference between the two groups (Figure 6A). The necrosis rate was 1.6% (4 of 245) in the EPC group and 2.0% (5 of 247) in the TPC group; the calculated OR was 0.72 (95%CI: 0.21–2.47), with an I^2 value of 0% and P = 0.61.

Three studies[13,17,24] that encompassed a total of 178 patients (85 patients in the EPC group and 93 in the TPC group) were analyzed, and we found that the groups did not differ with respect to ischemia (Figure 6B). The ischemia rate was 1.2% in the EPC group (one case of 85) and 4.3% in the TPC group (four cases of 93), for an OR of 0.40 (95%CI: 0.08–2.15), I^2 value of 0%, and P = 0.29.

Open approach after EPC vs TPC

We analyzed the incidence of PSH in two studies[14,26] that encompassed 478 patients (126 with EPC and 352 with TPC) (Figure 3C), and our results indicated a statistically significant difference favoring the extraperitoneal group. The PSH rate was 7.1% in the EPC (9 of 126 patients) *vs* 14.2% in the TPC (50 of 352 patients), for an OR of 0.40 (95%CI: 0.19–0.86), an I^2 of 0%, and P = 0.02.

Quality evaluation

This study adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3) to objectively evaluate the quality of the included trials using the risk-of-bias tool. The assessment focused on several key domains: (1) Random sequence generation; (2) Allocation concealment; (3) Blinding; (4) Incomplete outcome data; (5) Selective reporting; and (6) Other relevant biases.

Trials were classified as "high risk" if bias was identified in one or more critical domains, trials with low risk of bias across all critical domains were categorized as "low risk", and studies that did not clearly fall into either category were designated as "unclear" (the classification outcomes are illustrated in Figure 7). Any discrepancies among researchers were resolved through discussions involving the corresponding author.

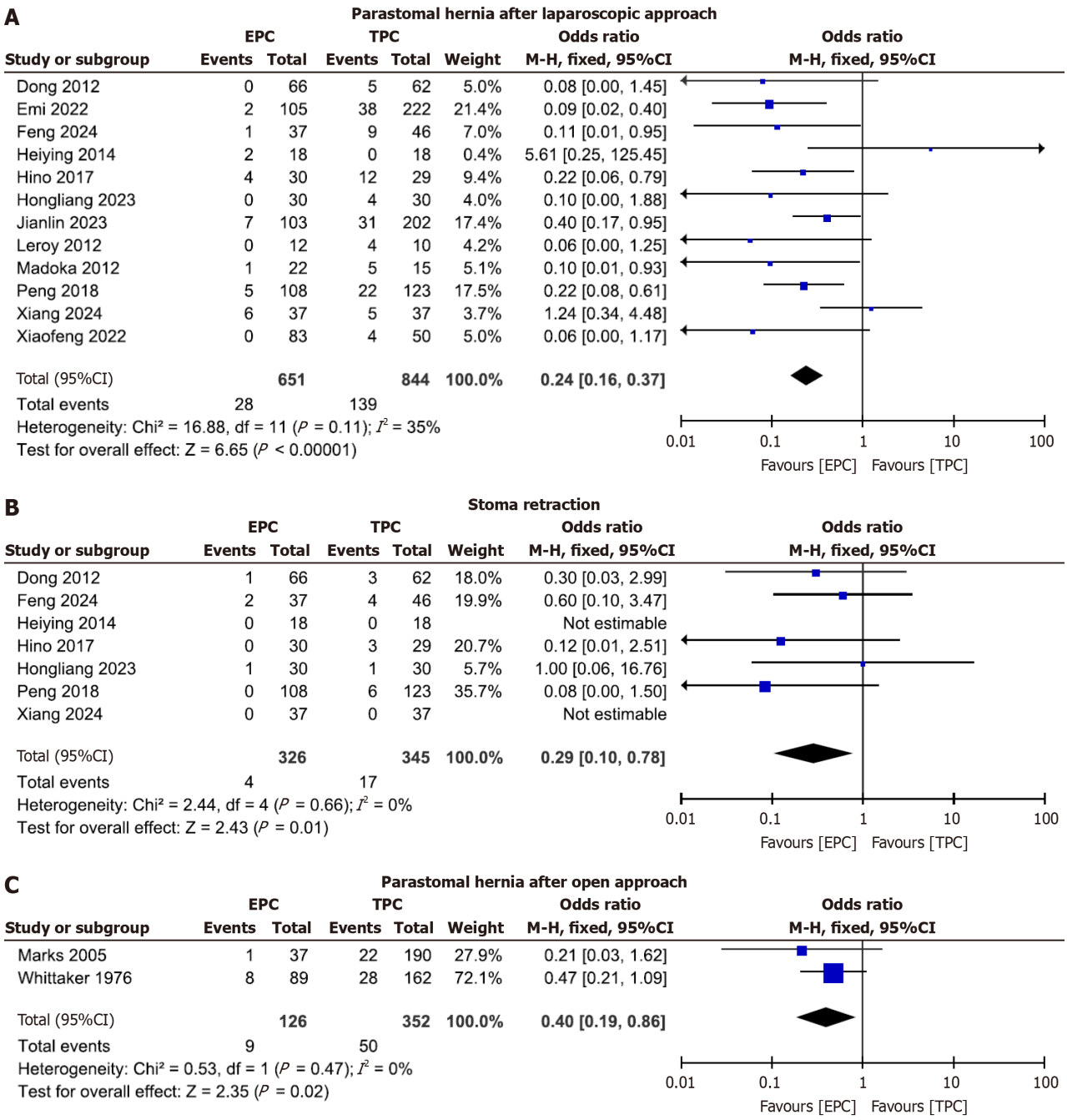

Figure 3 Forest plot of parastomal hernia after laparoscopic approach, stoma retraction, and parastomal hernia after open approach. A: Parastomal hernia after laparoscopic approach; B: Stoma retraction after laparoscopic approach; C: Parastomal hernia after open approach. EPC: Extraperitoneal colostomy; TPC: Transperitoneal colostomy.

Publication bias

We detected no evidence of publication bias, as all studies fell within the 95%CI boundaries. The symmetry of the funnel plot was statistically assessed using the Egger test and confirmed the absence of bias. For necrosis, the analysis yielded an OR of 0.72 (95%CI: 0.21–2.47; $P = 0.61$; $I^2 = 0\%$); while for ischemia, the OR was 0.40 (95%CI: 0.08–2.15; $P = 0.29$; $I^2 = 0\%$), demonstrating no significant evidence of bias as shown in Figure 8.

DISCUSSION

Colostomy complications include mucocutaneous separation, stoma retraction, infection, ischemia, necrosis, edema, prolapse, and PSH; with the most common of these being PSH. Traditional treatment has been effective for most PSH, but surgical intervention often results in suboptimal outcomes; thus, prevention is considered the best course of action. While previous investigations have shown that extraperitoneal stoma formation exerts beneficial effects[19], evidence-based

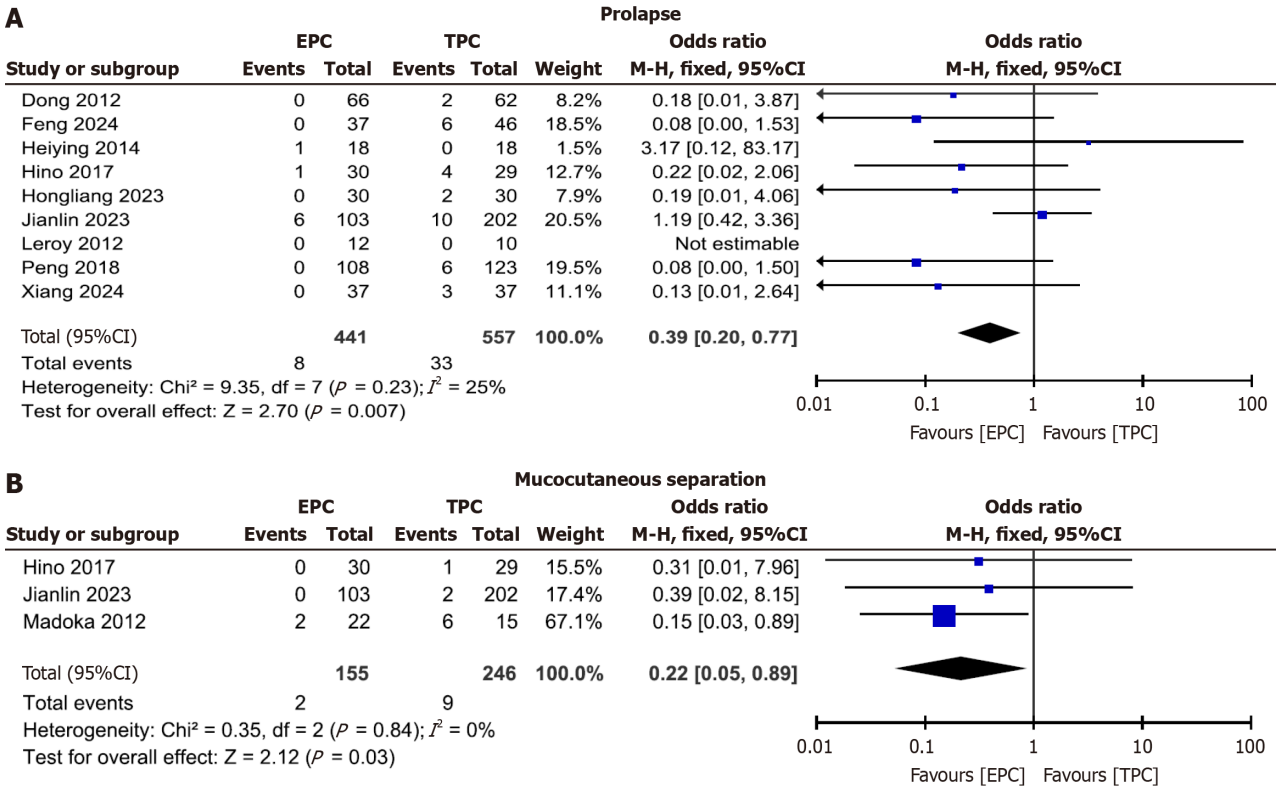

Figure 4 Forest plot of prolapse and mucocutaneous separation. A: Prolapse; B: Mucocutaneous separation after laparoscopic approach. EPC: Extraperitoneal colostomy; TPC: Transperitoneal colostomy.

medical data remain limited.

Although authors of previous meta-analyses attempted to address the limitations of small-scale studies and reported findings that differ from those of the current study, our analysis remains crucial. This importance stems from the significant amount of time that has elapsed since the last meta-analyses[9,10,27,28], and the inclusion of several cohort studies in our analysis that were not considered previously. Our meta-analysis notably includes data from 2363 patients, significantly exceeding the sample sizes of earlier studies that encompassed less than half of this number. Furthermore, our analysis emphasizes the reporting of PSH incidence rates based on distinct surgical approaches, thus providing a clearer perspective than previous research that often focused on laparoscopic or combined approaches[9,10,27,28]. By adopting this tailored approach, we offered a more detailed comparison and enhanced our ability to identify variations in outcomes across different surgical techniques.

Laparoscopic colostomy performed *via* the EPC route is often considered more technically demanding compared to the TPC route. However, congruent with findings from previous studies[15,16], our analysis did not reveal any differences in operative time or blood loss between the two approaches during laparoscopic surgery. Similarly, the authors of a separate meta-analysis also reported no notable differences between the techniques[10]. While Heiying *et al*[13] observed that the median operative time for the EPC route was approximately 10 min longer than for the TPC route, this difference was minimal and was deemed to be acceptable. This conclusion may be attributed to advancements in surgical techniques, procedural standardization, optimized patient selection, skilled surgical teams, and adherence to established clinical guidelines.

Recent developments have addressed the technical challenges associated with the EPC approach. For example, studies [29,30] have highlighted the use of a trocar-cannula system to create the extraperitoneal tunnel, simplifying the procedure by improving visualization and allowing for controlled tissue dissection. This technique reduces operative time and facilitates efficient creation of an EPC while maintaining satisfactory outcomes. Improved surgical skills and equipment, along with the selection of suitable patients and adherence to established protocols, likely contribute to the efficient performance of the EPC technique without significantly impacting operative outcomes relative to the TPC approach[29].

In the present study, the incidence of PSH was significantly lower with the EPC route compared to the TPC route in both laparoscopic and open surgical approaches ($P < 0.00001$ and $P = 0.02$, respectively), with our findings consistent with those of previous studies[27,28]. A primary contributing factor to PSH is the insufficient structural density at the junction between the colon and the abdominal wall that can compromise integrity and result in herniation. Supporting these results, a meta-analysis of 1048 patients revealed that the EPC route was associated with a lower incidence of PSH[9], congruent with our findings. However, other investigators reported no significant differences between the two routes[26, 31], potentially due to variations in surgical techniques or differences in follow-up durations. The literature presents varying perspectives on the clinical relevance of the EPC. While some authors argued that it exerted minimal impact on PSH incidence[32], others advocated for it as the preferred method for patients who required a permanent iliac colostomy [33]; in a more recent study, the authors continued to consider EPC as a viable option for such cases[34].

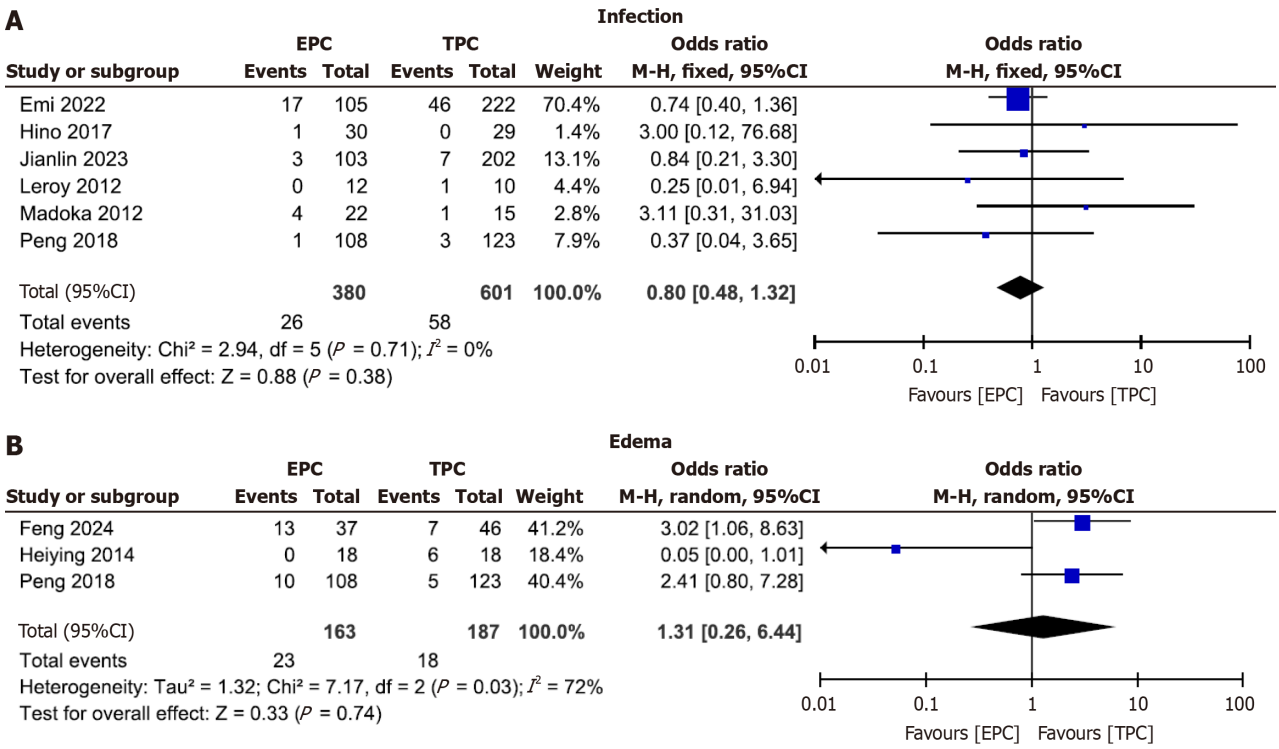

Figure 5 Forest plot of infection and edema. A: Infection; B: Edema after laparoscopic approach. EPC: Extraperitoneal colostomy; TPC: Transperitoneal colostomy.

Although we did not uncover any differences in the rates of necrosis (P = 0.61), ischemia (P = 0.29), edema (P = 0.74), or infection (P = 0.38), the EPC group demonstrated significantly lower incidences of prolapse (P = 0.007), stoma retraction (P = 0.01), and mucocutaneous separation (P = 0.03). Stoma retraction is commonly associated with colostomies and emergency procedures, with reported rates ranging from 1% to 30%[35]. While a previous meta-analysis showed no significant difference in retraction rates between the EPC and TPC approaches (P = 0.08)[28], our findings indicated a significant advantage for the EPC group (P = 0.01). This discrepancy may have been due to the limited number of studies available. Stoma retraction is often caused by inadequate bowel mobilization, resulting in mucocutaneous tension. Preventive measures therefore emphasize the importance of proper bowel mobilization, ensuring adequate blood supply to the stoma conduit; and creating an appropriately sized fascial aperture to facilitate smooth stoma delivery to the skin [35-37]. Stomal prolapse is a frequent late complication following stoma formation, with reported incidence rates in the literature ranging from 1.7% to 25%[38,39]. This condition occurs when increased intra-abdominal pressure (often due to a mobile or redundant intestine) causes the intestine to gradually protrude through the stoma site. The relationship between EPC and the risk of stomal prolapse thus remains a topic of debate. A meta-analysis by Lian *et al*[9] comparing EPC and TPC found no significant difference in prolapse rates (P = 0.38). However, in our study we identified a significantly lower rate of prolapse in the EPC group relative to the TPC group (P = 0.007), aligning with findings from prior research[27,28]. Techniques suggested to minimize stomal prolapse include extraperitoneal tunneling, fixation of the mesentery to the abdominal wall, and reducing the size of the stoma aperture[35]. Mucocutaneous separation, characterized by partial or complete detachment of the stoma mucosa from the peristomal skin, has an incidence rate of 3.7% to 9.7%[40-42], and is a complication that can lead to stoma retraction or stenosis, adversely affecting patient quality of life. To our knowledge, the present meta-analysis is the first-ever to report a significant difference in mucocutaneous separation rates between EPC and TPC groups (P = 0.03), with the EPC group showing a lower incidence. This novel finding underscores the potential advantage of the EPC technique in reducing mucocutaneous separation occurrence.

Impaired blood supply during stoma formation can lead to ischemia and necrosis, complications that are more commonly observed after colostomy compared to ileostomy[43]; and the reported incidence of vascular compromise ranges from 2.3 to 17%[44]. Key factors contributing to inadequate blood supply include high vascular ligation, damage to blood vessels, and a constricted abdominal aperture. Early identification of stomal ischemia is essential, as compromised vascularization may result in delayed complications[45]. We herein did not find any differences in the rates of necrosis (P = 0.61), ischemia (P = 0.29), or edema (P = 0.74), consistent with previous studies[10,28] that also reported no significant differences in ischemia or necrosis rates between EPC and TPC. Regarding other postoperative complications, Hamada *et al*[15] documented an infection rate of 18.2% for the EPC route compared to 6.6% for the TPC route, although this difference was not statistically significant. Variability in infection rates may stem from factors such as differences in anatomical exposure, surgical techniques, patient characteristics, wound care practices, postoperative management, and institutional protocols. Our meta-analysis also did not reveal any significant reduction in stoma infection risk with the EPC route using a laparoscopic approach; there was also no notable difference in the incidence of stoma edema. Although disparities were observed, the absence of statistical significance highlights the need for further research so that we may

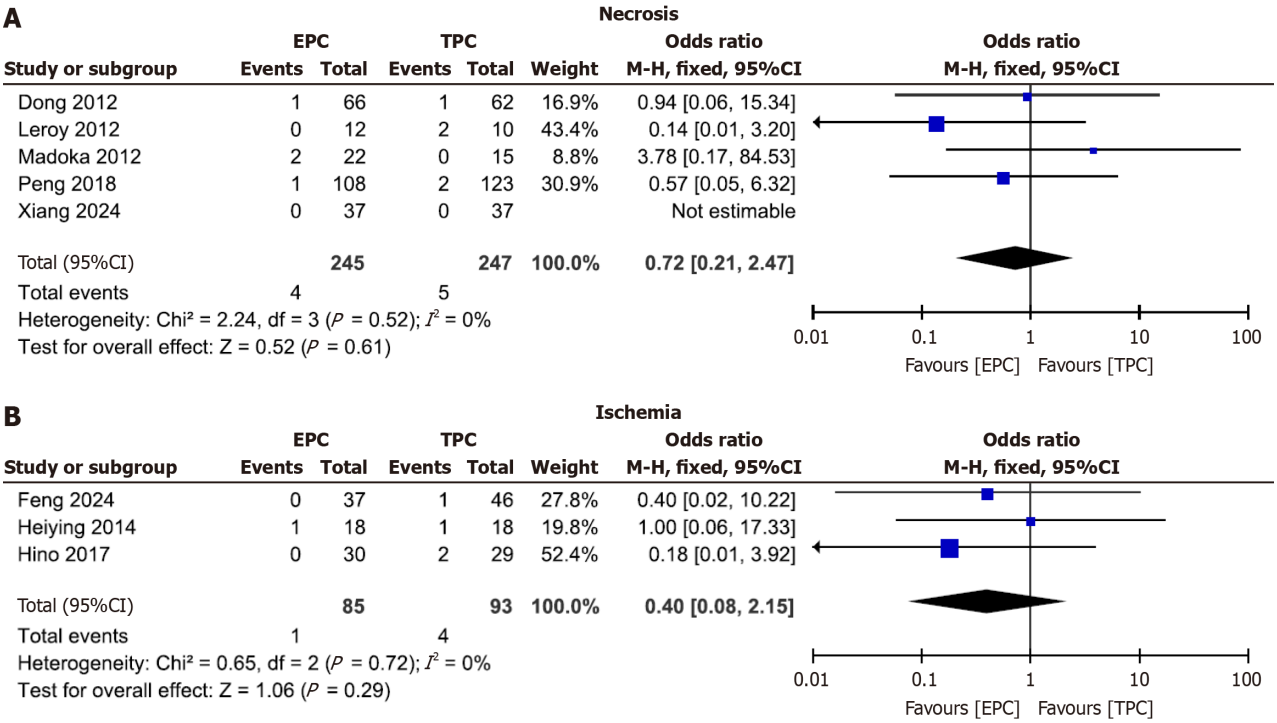

Figure 6 Forest plot of necrosis and ischemia. A: Necrosis; B: Ischemia. EPC: Extraperitoneal colostomy; TPC: Transperitoneal colostomy.

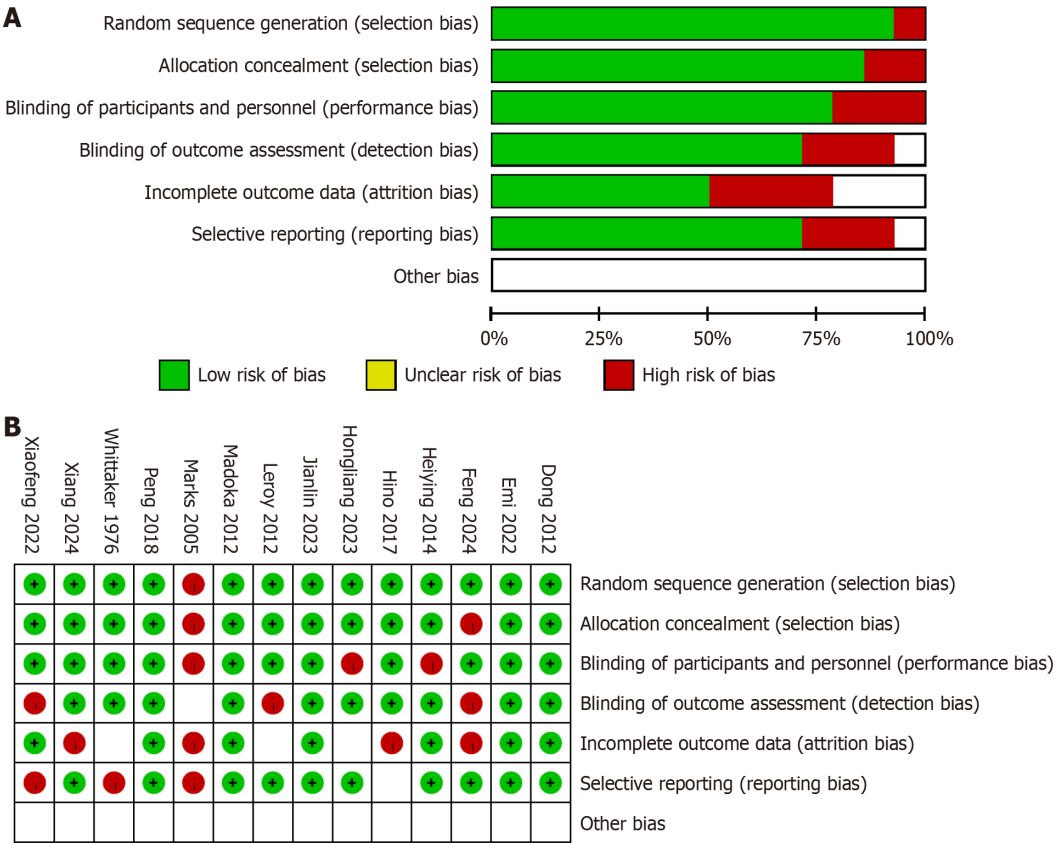

Figure 7 Quality assessment of included studies. A: Graph depicting the risk of bias by presenting the authors' assessments of each bias item as a percentage across all included studies; B: A summary of the bias assessments, detailing the authors' evaluations of each bias item for each study included in the review.

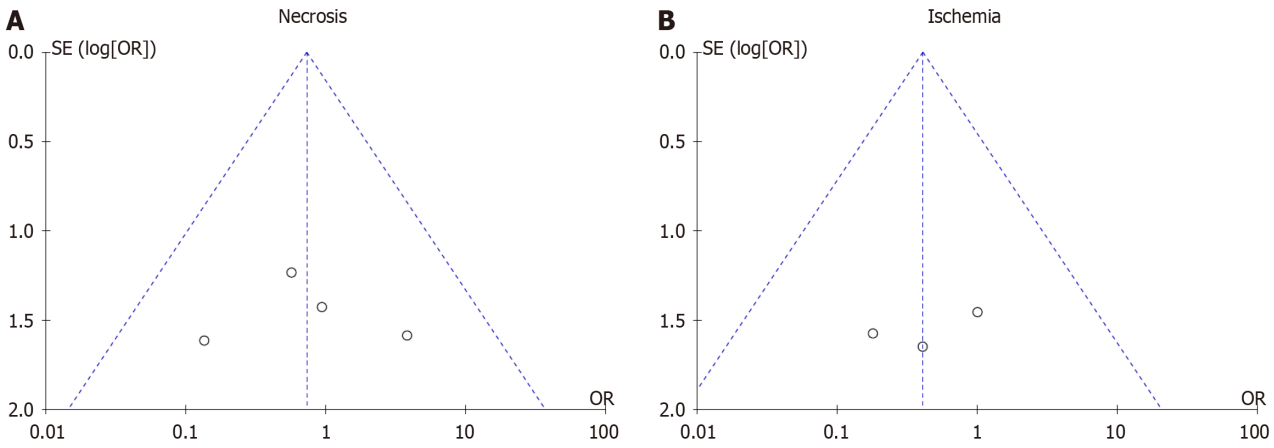

Figure 8 Funnel plot. A: Necrosis; B: Ischemia. OR: Odds ratio.

better understand the factors that influence postoperative infection rates following colostomy procedures.

The limitations we identified in our study include a predominance of RS over RCT, potentially limiting the power to adequately compare complications with low incidence rates. Additionally, there was variability in the selection of colostomy routes based on individual surgeon preferences and surgical contexts. Other limitations that could be considered include the diversity in patient populations across studies, variations in follow-up durations, the potential for publication bias, and differences in defining and reporting colostomy-related complications among included studies. Furthermore, the impact of factors such as post-operative care practices and healthcare settings on complication rates should be considered when interpreting the results.

CONCLUSION

In conclusion, the extraperitoneal route emerges as a promising strategy that can be implemented to mitigate specific stoma-related complications such as PSH and other related complications in colostomy surgery. By considering the extraperitoneal route, healthcare providers may be able to minimize the incidence of these complications, and this will ultimately lead to improved patient outcomes and quality of care. However, further research and ongoing assessment are necessary to confirm and build upon these findings, to improve patient care and treatment outcomes in the area of colostomy management.

FOOTNOTES

Author contributions: Isah AD and Wang X contributed equally as co-first authors. Isah AD, Shaibu Z and Yuan X were responsible for data collection and manuscript preparation; Dang CS and Wang X critically revised the manuscript for significant intellectual content, ensuring the accuracy and integrity of the work. All authors reviewed and approved the final manuscript.

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SCIENTOMETRICS

Global trends and research hotspots in esophageal strictures: A bibliometric study

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Abstract

BACKGROUND

Esophageal stricture is a prevalent condition affecting the digestive system, primarily marked by dysphagia and the obstruction of food passage through the esophagus. This narrowing of the esophageal lumen can significantly impact a person's ability to eat and drink comfortably, often leading to a decrease in nutritional intake and quality of life.

AIM

To explore the current research status and future trends of esophageal stricture through bibliometric analysis.

METHODS

Literature on esophageal stricture from 2004 to 2023 was retrieved from the Web of Science Core Collection. Statistical analysis was performed using Excel, VOSviewer, CiteSpace, and RStudio. This study provides data on annual production trends, countries/regions, influential authors, institutions, journals, references, and keywords.

RESULTS

The study included 1485 publications written by 7469 authors from 1692 institu-

tions across 66 countries/regions, published in 417 journals. The United States, China, and Japan are the major contributors to this field, with many quality papers. Song Ho-young, *Diseases of the Esophagus*, *Gastrointestinal Endoscopy*, and Mayo Clinic are the top authors, journals, co-cited journals, and institutions, respectively. The most frequent keywords are stent, endoscopy, management, etiology, and prevention; regenerative medicine, endoscopic injection, and autologous tissue transplantation are the latest research frontiers. These keywords reflect continuous advancements in technical innovation, treatment strategies, preventive measures in the esophageal stricture research field, and a sustained focus on improving patient prognosis. In contrast, the basic sciences were underrepresented.

CONCLUSION
This study provides an insightful analysis of the developments in the field of esophageal stricture over the past twenty years, with stent placement is currently a hot research topic.

Key Words: Esophageal stricture; Bibliometrics; Stents; VOSviewer; CiteSpace

Core Tip: This comprehensive bibliometric study offers an in-depth summary and analysis of 1485 publications authored by 7469 researchers from 66 countries, highlighting the leading contributions from the United States, China, and Japan. The study uncovers pivotal trends and emerging focal points in esophageal stricture research, particularly emphasizing breakthroughs in stent placement techniques, significant progress in regenerative medicine, the expanding role of endoscopic injection therapies, and the promising potential of autologous tissue transplantation. These insights are poised to influence and shape future therapeutic strategies and decision-making processes in the field.

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INTRODUCTION

Esophageal stricture is a prevalent digestive disorder characterized by narrowing of the esophagus, which impedes the passage of food and liquids. Esophageal strictures can be classified as either congenital or acquired based on their etiology and pathological features. Congenital esophageal stricture is an uncommon deformity characterized by narrowing of the lower esophagus due to intramural constriction[1]. In contrast, acquired esophageal stricture is caused primarily by fibrosis and scar formation in the esophageal wall and is typically induced by esophageal inflammation, ulcers, tumors, or surgery[2]. Clinically, treatment options for congenital esophageal stricture include dilation and surgical intervention. The treatment of acquired esophageal stricture encompasses a range of options, including pharmacological interventions, endoscopic procedures, and surgical techniques. The choice of treatment depends largely on the cause, severity of the stricture, patient's overall health, and anticipated quality of life. Epidemiological studies have shown a globally increasing incidence of this disease, which is likely attributed to various factors, including lifestyle changes, unbalanced diets, and environmental contamination[3]. This disease is most prevalent among middle-aged and elderly individuals, although children and adolescents may also be affected[4]. The diagnosis of esophageal stricture relies heavily on endoscopy and esophagography. Endoscopy allows direct visualization of the site, length of the stricture, and pathological changes in the esophageal wall[5]. Esophagography provides a comprehensive overview of the esophagus, including its morphology, location, and degree and extent of the stricture[6]. Esophageal manometry and esophageal dynamics are used to evaluate the functional status of the esophagus and determine the stricture etiology[7]. The pathogenesis of esophageal stricture is driven primarily by inflammatory and fibrotic processes. Inflammation in the esophageal wall causes tissue damage and cell death, triggering cellular proliferation and extracellular matrix deposition, ultimately leading to scarring fibrosis and narrowing of the esophagus[8]. Additionally, diseases such as gastroesophageal reflux disease (GERD), esophageal atresia, and esophageal cancer can result in esophageal stricture through similar mechanisms. Symptoms such as dysphagia, chest pain, and weight loss are indicative of esophageal stricture, with severity correlated with to the degree and extent of the stricture. In recent years, there has been a scarcity of guidelines in the field of esophageal stricture, leading to insufficient systematic guidance in clinical practice. Although case studies from individual institutions provide specialized knowledge, they do not offer a sufficient number of patients for effective care evaluation; this underscores the difficulties in advancing the knowledge of rare diseases. To address this gap, a comprehensive bibliometric approach has proven effective[9]. This method systematically analyzes the literature and identifies research hotspots and trends, providing a scientific foundation for future research and guideline development.

This study encompasses all research on esophageal stricture published over the past two decades. Various parameters, such as the number of publications, geographical distribution, authors, institutions, journals, references, and keywords, were analyzed[10,11]. This approach aims to provide a comprehensive understanding of the current state of research in this field. Additionally, a case of esophageal stricture caused by chemical corrosion was presented. Despite severe damage, two metal stents were successfully placed in the upper esophagus. Our objective is to produce a structured statistical report that offers a comprehensive overview, aids researchers in making informed decisions regarding esophageal stricture, and contributes to advancements in the field.

MATERIALS AND METHODS

Data source and literature inclusion criteria

The database is derived from Clarivate Analytics' Web of Science Core Collection (WoSCC) Science Citation Index Expanded. WoSCC is one of the most widely utilized databases in academic research, providing comprehensive data on numerous prominent journals and publications globally[12]. WoSCC was selected as the primary source for this study due to its extensive coverage of numerous academic journals and its frequent utilization by researchers. We searched WoSCC to identify all studies related to esophageal strictures with a data collection deadline of March 20, 2024. The time frame was limited to the last two decades, and the language to English. Publication types were restricted to articles and reviews, excluding conference abstracts, editorial material, letters, news reports, and book reviews. To ensure data accuracy and consistency, two independent reviewers conducted the search using the described method. Figure 1 and Supplementary Table 1 display the specific search strategy, and we exported all the obtained literature in plain text and Excel formats.

Data analysis and visualization

All graphs were obtained using Microsoft Excel 2021 (version 16.52), CiteSpace (version 6.1.6 R2, RRID: SCR_025121), VOSviewerr (version 1.6.18, RRID: SCR_023744), and RStudio software (version R-4.2.2, RRID: SCR_023744) with the bibliometric package[13]. The results are presented in three types of visualizations: Network with clusters, network with timeline, and clustering visualization. The literature information was imported into Microsoft Excel 2021, from which the following data were extracted for each publication: Author, title, journal source, the journal impact factor (derived from the Journal Citation Report 2023), keywords, citations, references, author's organization, author's country/region, co-cited authors, and co-cited journals.

CiteSpace (version 6.1.6 R2), developed by Dr. Chao-Mei Chen of Drexel University, United States. The software utilizes Java to visualize and analyze scientific references. CiteSpace is one of the most popular bibliometric tools for identifying evolving research topics and is commonly used to detect key authors, institutions, keywords, and co-cited references[13]. Bursts have been defined as a feature that has been frequently cited over time. Additionally, CiteSpace generates dual maps of journal citation relationships[14].

VOSviewer, another robust visualization tool, conducts scientific mapping analysis of publications[15]. It extracts essential information from high-frequency fields such as country/region, institution, author, journal, and keywords. Through bibliometric analysis, VOSviewer visually represents data in an easily understandable graphical format. Network maps are created to identify trends in research fields and measure the degree of collaboration. These visual network maps are interpreted based on four features: Size, color, distance, and connection line thickness. Nodes represent specific terms such as countries, authors, or keywords. Larger nodes indicate higher frequency, while smaller nodes indicate lower frequency. Different colors represent different sub-clusters within the field, the distance between nodes indicates correlation (closer nodes indicate higher correlation), and the thickness of the connection line represents the strength of collaboration between nodes. Data were standardized before being imported to VOSviewer to generate images, with different expressions related to the same author or keyword being unified to reduce bias.

Bibliometric analysis was conducted using the "bibliometrix" R package within the RStudio environment for most locally cited references and keywords. The bibliometrix package facilitated the extraction and analysis of high-frequency fields. Data standardization ensured consistency and accuracy, with visualizations like network maps used to identify research trends and measure collaboration strength. The features in the visualizations, such as node size, color, distance, and connection line thickness, were interpreted to represent frequency, clustering, correlation, and collaboration strength. Further validation of the visualized information was performed using VOSviewer and CiteSpace.

RESULTS

Analysis of annual publications and growth trends

Over the past two decades, research on esophageal stricture has shown a gradual overall increasing trend (Figure 2A), with the number of publications increasing from 43 in 2004 to 97 in 2023. This finding indicates growing attention and research interest in the field of esophageal stricture. Despite fluctuations in the growth rate, the overall trend demonstrates positive development, providing a solid foundation for future research and exploration (Figure 2B). This growth trend may reflect the academic community's increased emphasis on esophageal stricture issues and the rise in research investments, suggesting potential development opportunities and the importance of continued research in this field.

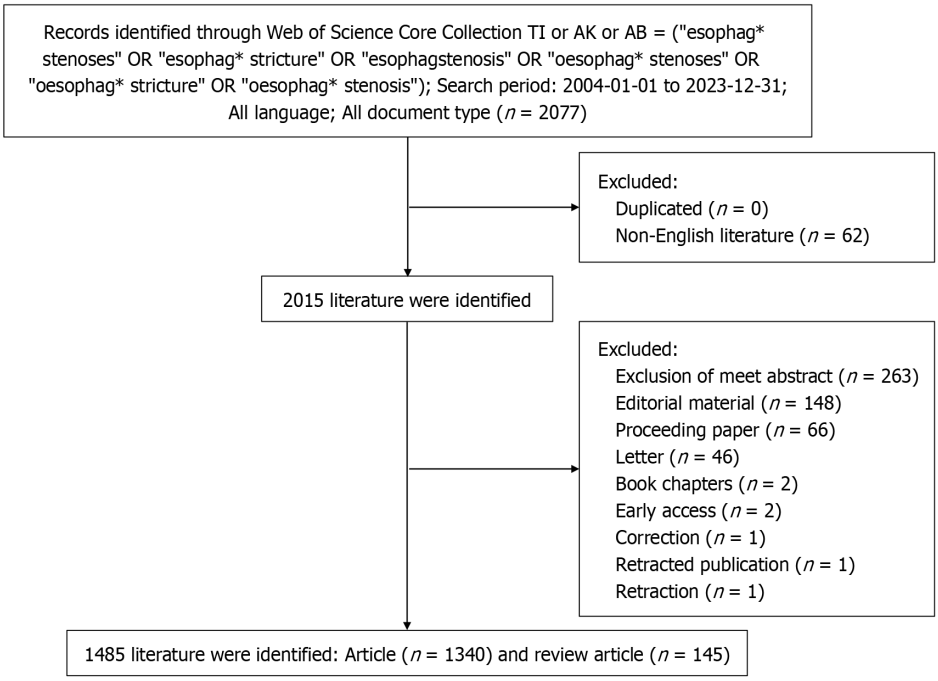


Figure 1 Literature data screening process and technology roadmap.

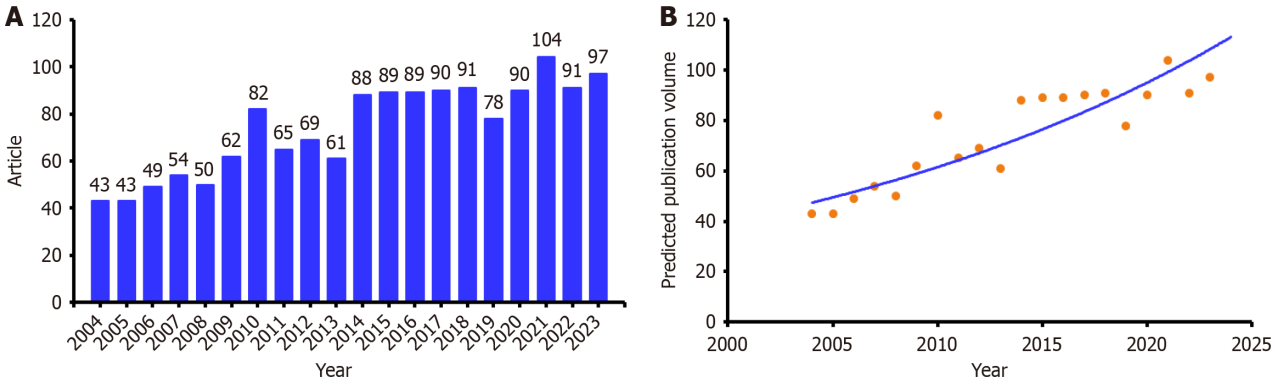


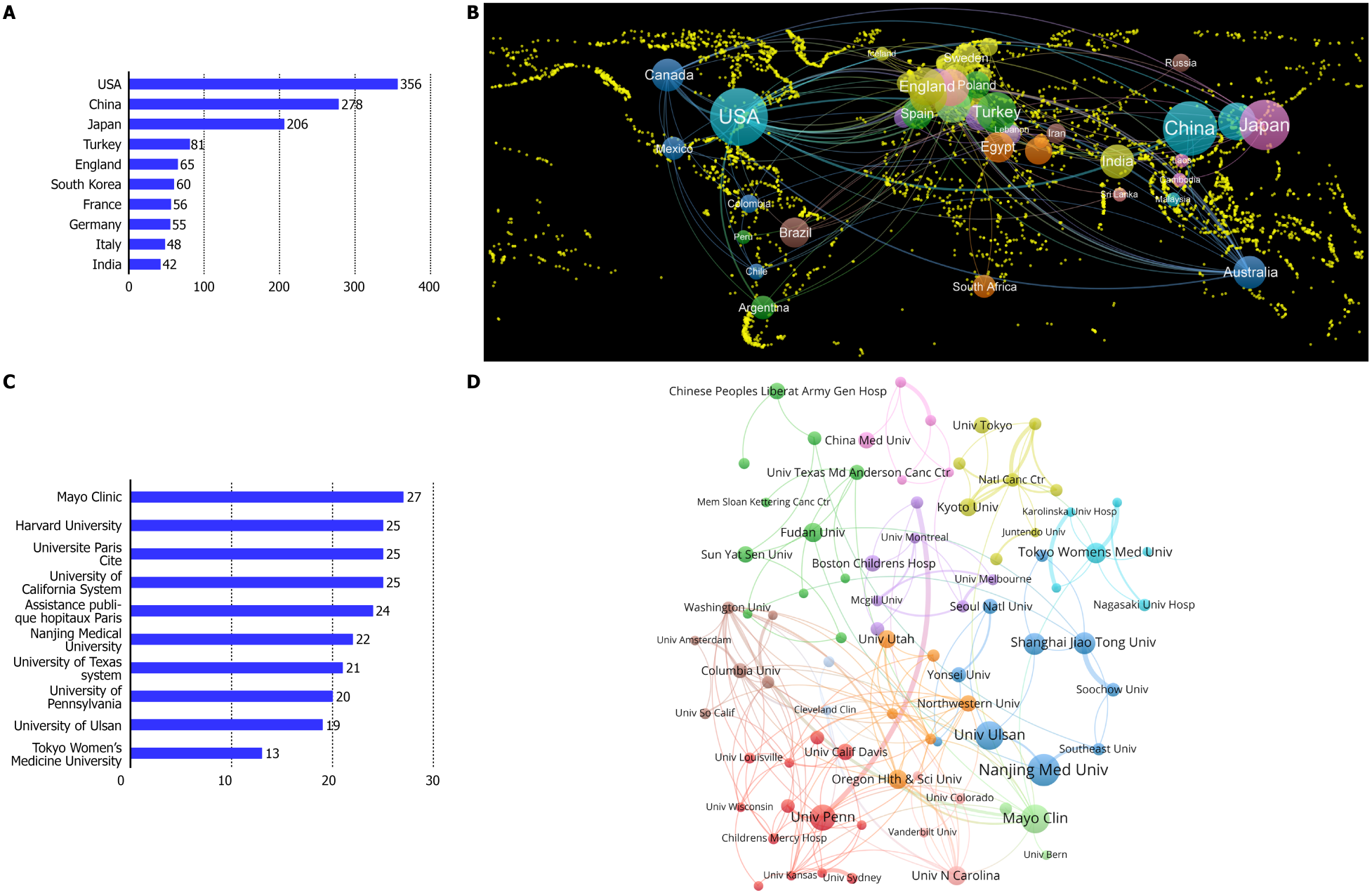
Figure 2 Publication trends in the field of esophageal stricture during 2004 and 2023. A: Annual publication volume; B: Curves of growth trends.

Analysis of countries/regions

The research papers in this field originate from 66 countries/regions, with the United States contributing the most (356 papers, accounting for 23.98%), followed by China (278 papers, 18.72%), Japan (206 papers, 13.87%), Turkey (81 papers, 5.45%), and England (65 papers, 4.38%) (Figure 3A). In terms of citations, the United States leads with 10740, followed by Japan (5749), China (2620), France (1754), and Germany (1601). With respect to centrality, the United States ranks first (0.26), followed by England (0.21), Japan (0.10), Denmark (0.10), and Italy (0.08). Supplementary Table 2 Lists the publications, citation counts, and centralities of these 66 countries. Using VOSviewer, a collaboration and global distribution map was created based on the cooperation between countries. Figure 3B displays a visual map of collaborations between different countries, where the nodes size indicates the connection strength. Larger nodes represent stronger connections and tighter cooperation. The United States shows the most active collaboration with other countries, with the highest total link strength (TLS = 76), and the closest cooperation is between the United States and China (TLS = 21).

Analysis of institutions

A total of 1692 institutions have contributed to this research field. As shown in Figure 3C, the top 10 institutions ranked by the number of publications are led by Mayo Clinic (27 publications), Harvard University (25 publications), Université Paris Cité (25 publications), the University of California System (25 publications), and Assistance Publique Hôpitaux Paris (24 publications). In terms of citation counts, Mayo Clinic ranks first with 2169 citations, Harvard University ranks second with 1525 citations, and the University of California System ranks third with 1475 citations. Supplementary Table 3 Lists the top 60 institutions by publication count, citation count, and centrality. VOSviewer was used to analyze the collaboration between institutions. Figure 3D presents a visual map of collaboration between different institutions, with the thickness of the connecting lines representing the strength of cooperation. Among the institutions, the Mayo Clinic (TLS =


A
USA 356
China 278
Japan 206
Turkey 81
England 65
South Korea 60
France 56
Germany 55
Italy 48
India 42
0 100 200 300 400
B
Canada
USA
Mexico
Colombia
Peru
Brazil
Chile
Argentina
Iceland
Sweden
England
Poland
Spain
Turkey
Lebanon
Iran
Egypt
Russia
China
Japan
India
Laos
Cambodia
Sri Lanka
Malaysia
South Africa
Australia
C
Mayo Clinic 27
Harvard University 25
Universite Paris Cite 25
University of California System 25
Assistance publique hopitaux Paris 24
Nanjing Medical University 22
University of Texas system 21
University of Pennsylvania 20
University of Ulsan 19
Tokyo Women's Medicine University 13
0 10 20 30
D
Chinese Peoples Liberat Army Gen Hosp
Univ Tokyo
China Med Univ
Univ Texas Md Anderson Canc Ctr
Natl Canc Ctr
Mem Sloan Kettering Canc Ctr
Kyoto Univ
Karolinska Univ Hosp
Fudan Univ
Univ Montreal
Juntendo Univ
Sun Yat Sen Univ
Boston Childrens Hosp
Tokyo Womens Med Univ
Univ Melbourne
Mcgill Univ
Washington Univ
Seoul Natl Univ
Nagasaki Univ Hosp
Univ Amsterdam
Univ Utah
Shanghai Jiao Tong Univ
Columbia Univ
Yonsei Univ
Soochow Univ
Univ So Calif
Cleveland Clin
Northwestern Univ
Univ Ulsan
Univ Louisville
Univ Calif Davis
Southeast Univ
Nanjing Med Univ
Oregon Hlth & Sci Univ
Univ Colorado
Univ Wisconsin
Univ Penn
Mayo Clin
Childrens Mercy Hosp
Vanderbilt Univ
Univ Bern
Univ Kansas
Univ Sydney
Univ N Carolina

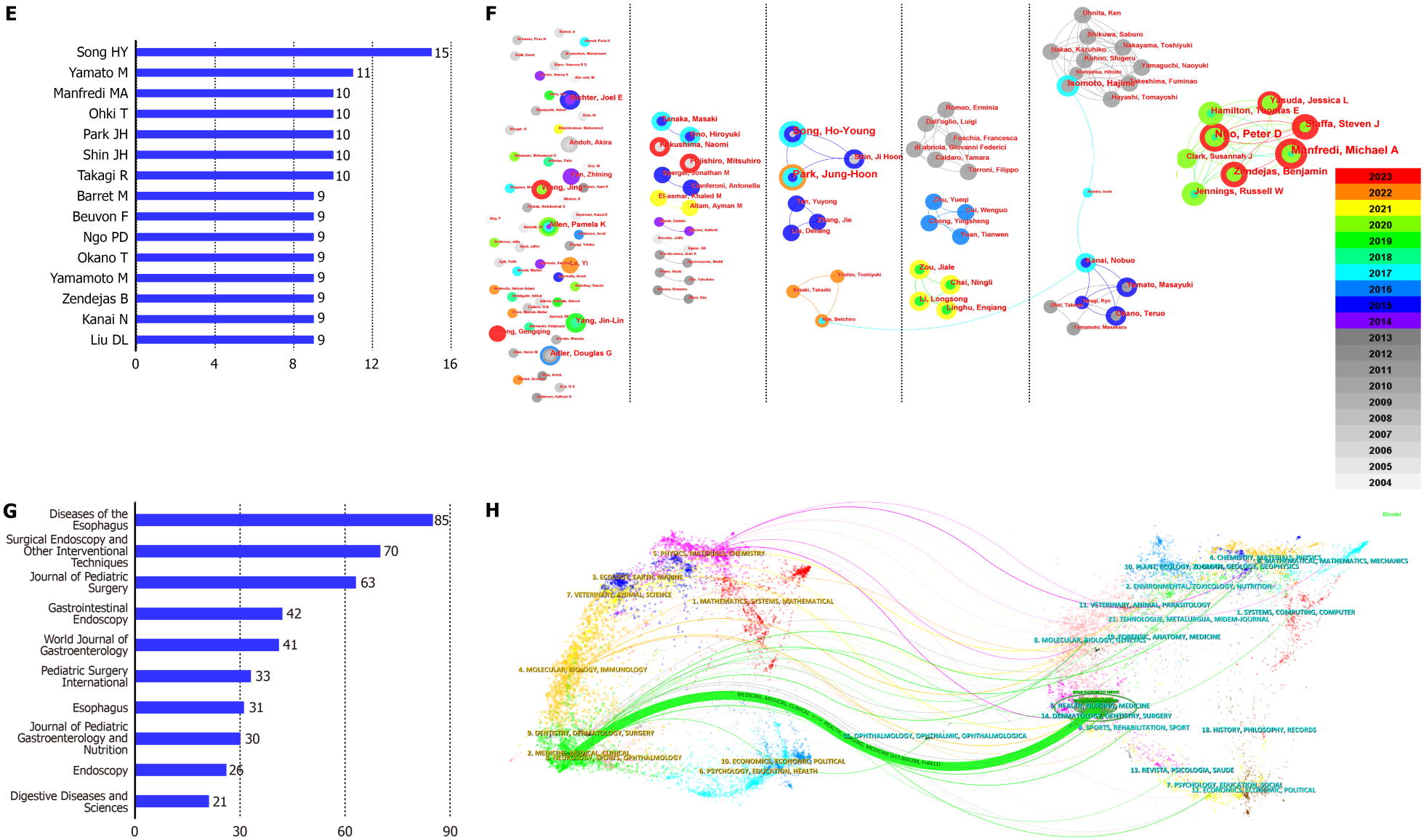


Figure 3 Visualization of the origin country, institutions, authors, and journals of publications. A: The top 10 fruitful countries; B: Distribution map of collaboration between countries; C: The top 10 fruitful institutions; D: Distribution map of collaboration between institutions; E: The top 10 fruitful authors; F: Distribution map of collaboration between authors; G: The top 10 fruitful journals; H: The dual-map overlay of journals.

47) and the University of Pennsylvania (TLS = 44) maintain close collaboration with each other.

Analysis of authors

Many scholars are dedicated to researching esophageal strictures. Using the analysis tools of the WoSCC, 7469 authors were found to have participated in this field. Supplementary Table 4 Lists the top 15 authors ranked by publication volume. Figure 3E shows that Song Ho-Young (Song HY) is the leading author, with 15 articles. Figure 3F shows the collaborative relationships among the top authors. Song HY, Park Jung-Hoo (Park JH, publication = 10), and Shin Ji Hoon (Shin JH, publication = 10), affiliated with the University of Ulsan, are involved in a collaborative endeavor focused on fluoroscopically guided significant balloon dilatation for the treatment of congenital esophageal stenosis. Yamato Masayuki (Yamato M, publication = 11), Ohki Takeshi (Ohki T, publication = 10), Takagi, Ryo (Takagi R, publication = 10), Okano Teruo (Okano T, publication = 9), Yamamoto Masakazu (Yamamoto M, publication = 9) and Kanai, Nobuo (Kanai N, publication = 9) from Tokyo Women's Medical University are prominent in research on tissue engineering and regenerative medicine. Manfredi Michael A (Manfredi MA, publication = 10), Ngo Peter D (Ngo PD, publication = 9), and Zendejas Benjamin (Zendejas B, publication = 9) from Boston Children's Hospital primarily focus on pediatric esophageal strictures. Overall, these researchers cover a range of clinical studies on esophageal strictures and emerging fields in regenerative medicine. Notably, research on the pathophysiological mechanisms of esophageal strictures is relatively rare.

Analysis of journals

A total of 417 journals have published these publications. Among them, 224 journals (53.72%) published only one related article, 141 journals (33.81%) published between two and five, and 52 journals (12.47%) published six or more articles. Figure 3G displays the ten most productive journals. *Diseases of the Esophagus* (86 articles) is the leading journal, followed by *Surgical Endoscopy and other Interventional Techniques* (70 articles). The top 10 most productive journals account for 30% of the total publications in this field. The mean impact factor of these top 10 journals is 3.96. Citation analysis revealed that 33 journals had more than 100 citations (Supplementary Table 5), with *Gastrointestinal Endoscopy* leading with 2128 citations. To examine the distribution of citing and cited journals, we employed a dual map overlay analysis (Figure 3H). The map on the left represents the citing journals, whereas the map on the right represents the cited journals. The labels on the map indicate the topics covered by the journals, and colorful curves illustrate the reference paths from the citing journals (*e.g.*, medicine, medical and clinical) to the cited journals (*e.g.*, health, nursing, and medicine).

Analysis of highly cited and co cited publications

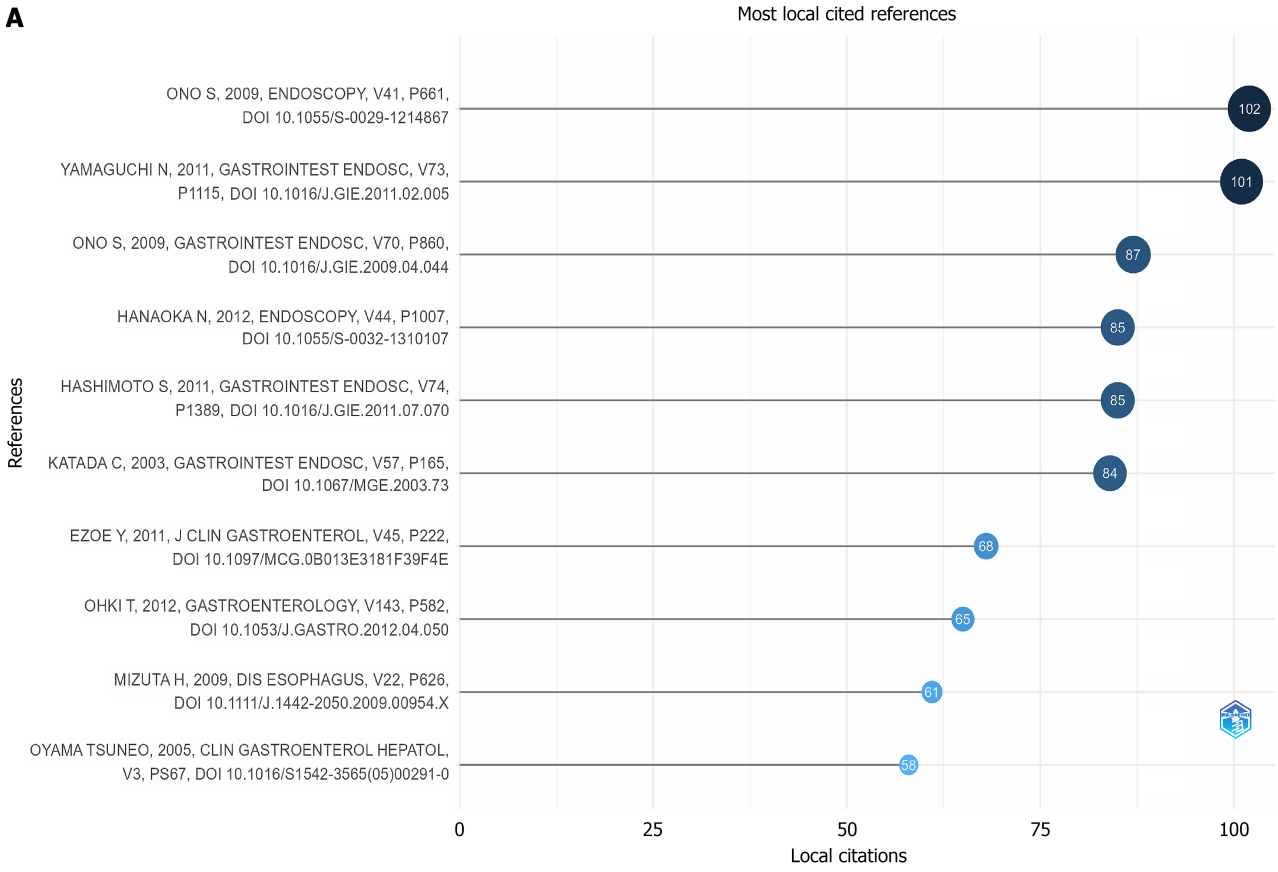
Among the 1485 publications, the top 10 most cited articles focused on endoscopic evaluation (Supplementary Table 6), treatment methods (*e.g.*, radiofrequency ablation by Shaheen *et al*[16]), eosinophilic esophagitis (*e.g.*, Hirano *et al*[17]), and tissue engineering (*e.g.*, Ohki *et al*[18]), predominantly from the United States and Japan. The United States emphasizes Barrett's esophagus and GERD, whereas Japan focuses on endoscopic submucosal dissection (ESD) and tissue engineering. Articles in prestigious journals (*New England Journal of Medicine*, *Gut*, and *Gastroenterology*) such as Shaheen *et al*'s study[16] with 1007 citations, illustrating leadership in the field, have high scientific impact. Seminal works such as Kovesi *et al*'s paper[19] demonstrate enduring academic value, whereas emerging technologies, including ESD and tissue engineering, indicate the field's progress toward precise treatments. Key studies, such as Yamaguchi *et al*'s work[20] on oral prednisone post-ESD and Stadlhuber *et al*'s work[21] on prosthesis complications, reflect the integration of basic research with clinical applications and interdisciplinary collaboration.

Figure 4A highlights influential papers published between 2003 and 2012, with peaks in 2009 and 2011. Notably, two works by Ono *et al*[22] in 2009 and one by Yamaguchi *et al*[20] in 2011 are foundational to the field. Citation bursts (Figure 4B) indicate widespread attention from 2004 to 2023, with a focus on endoscopic techniques such as ESD and radiofrequency ablation, as seen in studies by Ono *et al*[22] in 2009 and Takahashi *et al*[23] in 2011. Innovative works, such as Ohki *et al*'s research[18] in 2012 on tissue-engineered applications and Liacouras *et al*'s study[24] in 2011 of eosinophilic esophagitis, significantly influence academia and clinical practice. These impactful studies shape research directions and directly inform treatment strategies, such as the use of oral prednisone and tissue-engineered cell sheets.

Analysis of keywords

Keyword analysis *via* VOSviewer identified seven clusters related to esophageal stricture research (Figure 5A). Cluster 1 (red) included keywords such as Barrett's esophagus, eosinophilic esophagitis, and esophageal adenocarcinoma, reflecting diseases associated with esophageal stricture. Cluster 2 (green) focuses on regenerative medicine, cell sheets, and scaffolds, highlighting new treatment applications. Cluster 3 (blue) covers methods such as endoscopic dilation and steroid injection for treating strictures. Cluster 4 (yellow) included terms such as proton pump inhibitors and collagen, detailing substances used in treatment. Cluster 5 (purple) relates to clinical trials and efficacy. Cluster 6 (light blue) reflects patient populations and experimental models, whereas Cluster 7 (orange) highlights diagnostic methods such as endoscopy and barium swallow. The regenerative medicine cluster has emerged recently, whereas other clusters, such as disease conditions and treatment methods, remain prominent. The research hotspots and time distributions of different clusters are shown in Figure 5B and C. Clusters involving regenerative medicine and tissue engineering have emerged as new fields in recent years, whereas the clusters related to diseases and conditions of esophageal stricture, methods for treating and preventing esophageal stricture, treatment populations, experimental subjects, and diagnostic and examination procedures for patients with esophageal stricture have remained hotspots.

Keyword trends over time reveal important insights (Figure 5D). Recent research hotspots include "postoperative stricture", "stent placement", and "chemoradiotherapy". Earlier trends focused on "photodynamic therapy" and

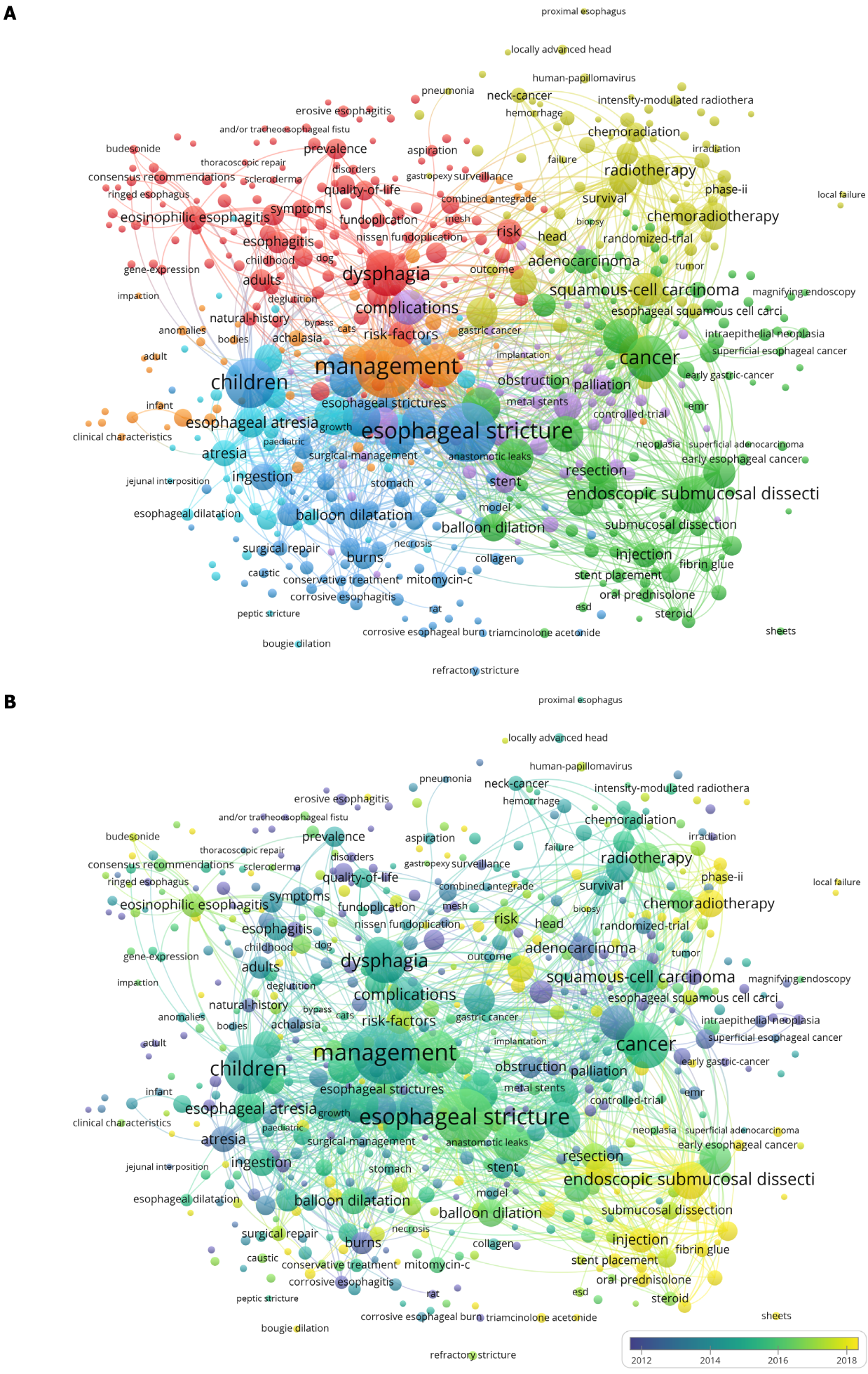


B

Top 25 references with the strongest citation bursts

References	Year	Strength	Begin	End	2004-2023
Repici A, 2004, GASTROINTEST ENDOSC, V60, P513, DOI 10.1016/S0016-5107(04)01882-6, DOI	2004	8.47	**2007**	2009	
Evrard S, 2004, GASTROINTEST ENDOSC, V60, P894, DOI 10.1016/S0016-5107(04)02278-3, DOI	2004	7.25	**2007**	2009	
Nieponice A, 2009, GASTROINTEST ENDOSC, V69, P289, DOI 10.1016/j.gie.2008.04.022, DOI	2009	7.85	**2010**	2014	
Siersema PD, 2008, NAT CLIN PRACT GASTR, V5, P142, DOI 10.1038/ncpgasthep1053, DOI	2008	6.67	**2010**	2013	
Ono S, 2009, GASTROINTEST ENDOSC, V70, P860, DOI 10.1016/j.gie.2009.04.044, DOI	2009	9.25	**2011**	2014	
Ono S, 2009, ENDOSCOPY, V41, P661, DOI 10.1055/s-0029-1214867, DOI	2009	8.76	**2011**	2014	
Mizuta H, 2009, DIS ESOPHAGUS, V22, P626, DOI 10.1111/j.1442-2050.2009.00954.x, DOI	2009	6.81	**2011**	2014	
Yamaguchi N, 2011, GASTROINTEST ENDOSC, V73, P1115, DOI 10.1016/j.gie.2011.02.005, DOI	2011	13.44	**2012**	2016	
Hashimoto S, 2011, GASTROINTEST ENDOSC, V74, P1389, DOI 10.1016/j.gie.2011.07.070, DOI	2011	10.15	**2012**	2016	
Ezoe Y, 2011, J CLIN GASTROENTEROL, V45, P222, DOI 10.1097/MCG.0b013e3181f39f4e, DOI	2011	8.32	**2012**	2016	
Liacouras C, 2011, J ALLERGY CLIN IMMUN, V128, P3, DOI 10.1016/j.jaci.2011.02.040, DOI	2011	8.63	**2013**	2016	
Hanaoka N, 2012, ENDOSCOPY, V44, P1007, DOI 10.1055/s-0032-1310107, DOI	2012	13.01	**2014**	2017	
Ohki T, 2012, GASTROENTEROLOGY, V143, P582, DOI 10.1053/j.gastro.2012.04.050, DOI	2012	10.62	**2014**	2017	
Sato H, 2013, GASTROINTEST ENDOSC, V78, P250, DOI 10.1016/j.gie.2013.01.008, DOI	2013	8.34	**2014**	2018	
Takahashi H, 2011, ENDOSCOPY, V43, P184, DOI 10.1055/s-0030-1256109, DOI	2011	6.66	**2015**	2016	
Takahashi H, 2015, BMC GASTROENTEROL, V15, P0, DOI 10.1186/s12876-014-0226-6, DOI	2015	7.63	**2016**	2020	
Iizuka T, 2015, ENDOSCOPY, V47, P341, DOI 10.1055/s-0034-1390770, DOI	2015	7.15	**2016**	2020	
Kataoka M, 2015, ENDOSC INT OPEN, V3, PE113, DOI 10.1055/s-0034-1390797, DOI	2015	6.57	**2017**	2019	
Hanaoka N, 2016, ENDOSC INT OPEN, V4, PE354, DOI 10.1055/s-0042-100903, DOI	2016	6.7	**2018**	2021	
Iizuka T, 2018, DIS ESOPHAGUS, V31, P0, DOI 10.1093/dote/dox140, DOI	2018	8.17	**2019**	2023	
Liao ZL, 2018, GASTROINTEST ENDOSC, V88, P543, DOI 10.1016/j.gie.2018.04.2349, DOI	2018	7.39	**2019**	2023	
Chai NL, 2018, WORLD J GASTROENTERO, V24, P1046, DOI 10.3748/wjg.v24.i9.1046, DOI	2018	6.61	**2019**	2023	
Nagami Y, 2018, DIGEST ENDOSC, V30, P198, DOI 10.1111/den.12946, DOI	2018	6.61	**2019**	2023	
Chu Y, 2019, SURG ENDOSC, V33, P1244, DOI 10.1007/s00464-018-6404-9, DOI	2019	8.16	**2020**	2023	
Sami SS, 2018, GUT, V67, P1000, DOI 10.1136/gutjnl-2017-315414, DOI	2018	7.51	**2021**	2023	

Figure 4 The citation and co-cited references network visualization map of references from 2004 to 2023. A: Most local cited references; B: The top 25 co-cited references with the strongest citation bursts from 2004 to 2023.


A
proximal esophagus
locally advanced head
human-papillomavirus
pneumonia
neck-cancer
intensity-modulated radiothera
erosive esophagitis
hemorrhage
and/or tracheoesophageal fistu
chemoradiation
budesonide
prevalence
aspiration
irradiation
thoracoscopic repair
failure
disorders
radiotherapy
consensus recommendations
scleroderma
gastropexy surveillance
quality-of-life
phase-ii
ringed esophagus
combined antegrade
survival
local failure
symptoms
eosinophilic esophagitis
fundoplication
mesh
biopsy
chemoradiotherapy
risk
head
esophagitis
nissen fundoplication
randomized-trial
childhood
dog
adenocarcinoma
tumor
gene-expression
dysphagia
outcome
adults
squamous-cell carcinoma
magnifying endoscopy
impaction
deglutition
complications
esophageal squamous cell carci
natural-history
bypass
cats
anomalies
risk-factors
gastric cancer
intraepithelial neoplasia
bodies
achalasia
superficial esophageal cancer
adult
implantation
cancer
management
obstruction
palliation
early gastric-cancer
children
esophageal strictures
metal stents
emr
infant
controlled-trial
esophageal atresia
growth
esophageal stricture
clinical characteristics
paediatric
neoplasia
superficial adenocarcinoma
atresia
surgical-management
anastomotic leaks
early esophageal cancer
ingestion
stomach
resection
jejunal interposition
stent
endoscopic submucosal dissecti
esophageal dilatation
model
balloon dilatation
balloon dilation
submucosal dissection
surgical repair
necrosis
injection
burns
collagen
fibrin glue
caustic
conservative treatment
mitomycin-c
stent placement
corrosive esophagitis
oral prednisolone
peptic stricture
rat
esd
steroid
corrosive esophageal burn
triamcinolone acetonide
sheets
bougie dilation
refractory stricture
B
proximal esophagus
locally advanced head
human-papillomavirus
pneumonia
neck-cancer
intensity-modulated radiothera
erosive esophagitis
hemorrhage
and/or tracheoesophageal fistu
chemoradiation
budesonide
prevalence
aspiration
irradiation
thoracoscopic repair
failure
disorders
radiotherapy
consensus recommendations
scleroderma
gastropexy surveillance
quality-of-life
phase-ii
ringed esophagus
combined antegrade
survival
local failure
symptoms
eosinophilic esophagitis
fundoplication
mesh
biopsy
chemoradiotherapy
risk
head
esophagitis
nissen fundoplication
randomized-trial
childhood
dog
adenocarcinoma
tumor
gene-expression
dysphagia
outcome
adults
squamous-cell carcinoma
magnifying endoscopy
impaction
deglutition
complications
esophageal squamous cell carci
natural-history
bypass
cats
anomalies
risk-factors
gastric cancer
intraepithelial neoplasia
bodies
achalasia
superficial esophageal cancer
adult
implantation
cancer
management
obstruction
palliation
early gastric-cancer
children
esophageal strictures
metal stents
emr
infant
controlled-trial
esophageal atresia
growth
esophageal stricture
clinical characteristics
paediatric
neoplasia
superficial adenocarcinoma
atresia
surgical-management
anastomotic leaks
early esophageal cancer
ingestion
stomach
resection
jejunal interposition
stent
endoscopic submucosal dissecti
esophageal dilatation
model
balloon dilatation
balloon dilation
submucosal dissection
surgical repair
necrosis
injection
burns
collagen
fibrin glue
caustic
conservative treatment
mitomycin-c
stent placement
corrosive esophagitis
oral prednisolone
peptic stricture
rat
esd
steroid
corrosive esophageal burn
triamcinolone acetonide
sheets
bougie dilation
refractory stricture
2012
2014
2016
2018

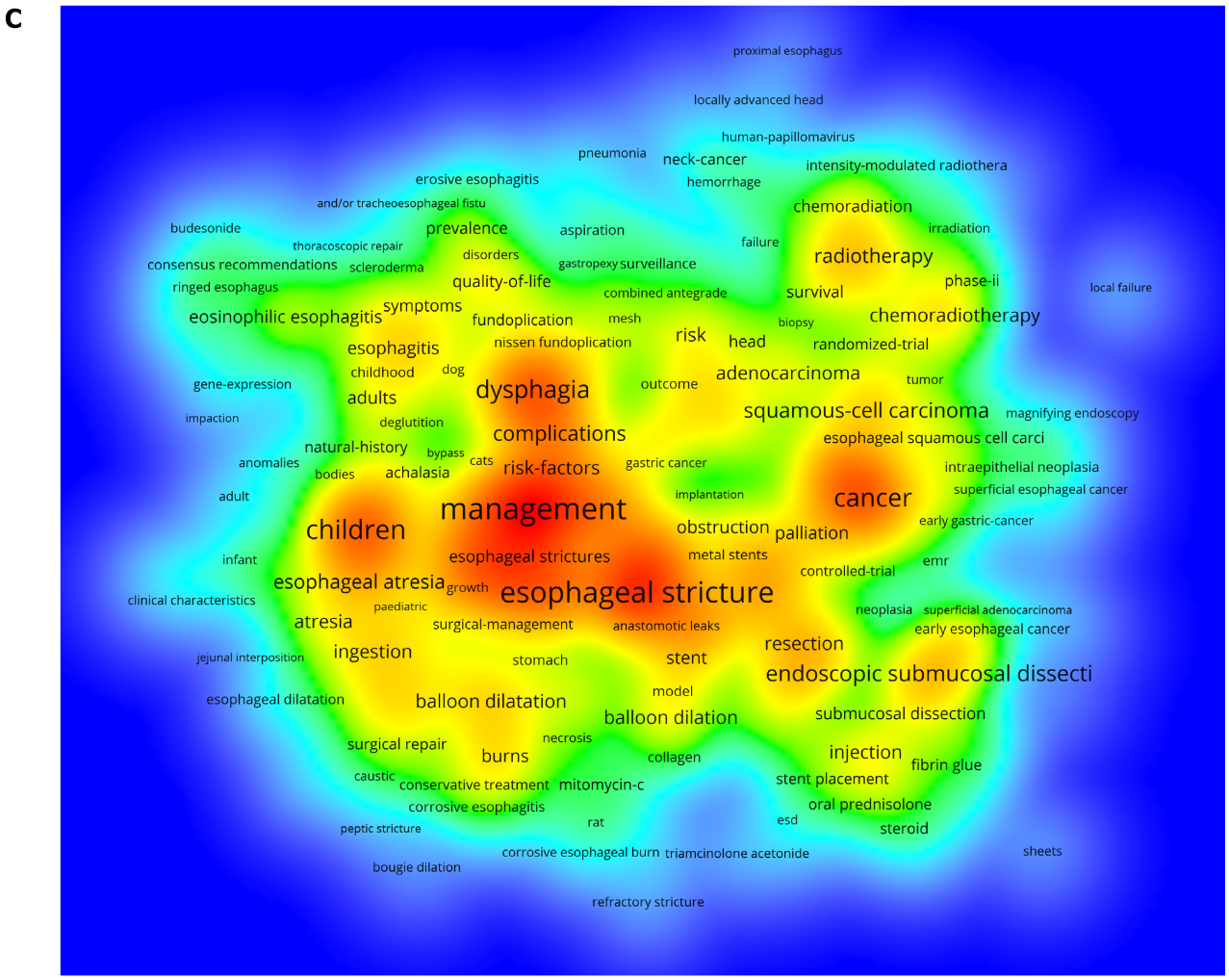


Figure 5 The co-occurrence network visualization map of keywords. A: Keywords co-occurrence network with different clusters; B: Keywords co-occurrence network with average publication year; C: Keywords density map according to the mean frequency of occurrences (orange indicated the highest

frequency); D: Evolutionary trajectory of "keywords plus" terms over time.

"omeprazole", with more topics such as "Barrett's esophagus" and "adenocarcinoma" emerging from 2007-2014. From 2015 onward, areas such as "postoperative stricture" and "balloon dilatation" gained attention. New topics such as "cell sheets" and "ESD" are now emerging. The analysis indicates ongoing interest in clinical treatments, including "stent placement" and "chemoradiotherapy", as well as a sustained focus on esophageal cancers and treatment efficacy.

DISCUSSION

General information

Bibliometric analysis is a valuable tool for assessing global research trends and hotspots across various disciplines[25,26]. Our study analyzed 1485 articles on esophageal stricture from the WoSCC database published over the past two decades. The results indicated a steady increase in publications from 2004 to 2009, followed by a significant surge in 2010, likely attributed to the adoption of endoscopic mucosal resection and ESD for early esophageal tumors[27]. These innovations highlight the incidence and management of postoperative esophageal strictures, which remain pivotal for future clinical practice and research. Despite annual fluctuations, the number of publications has shown a general upward trend. The United States leads in publications, citations, and collaborations, reflecting its robust health care infrastructure and academic resources. Similarly, China and Japan exhibit high research activity, driven by their large patient populations and aging demographics, respectively. Key journals such as *Diseases of the Esophagus* and *Surgical Endoscopy* focus on esophageal diseases, with significant citation networks emphasizing the role of endoscopic techniques. However, interdisciplinary collaborations remain limited, highlighting an area for growth. Influential researchers and institutions, such as Song HY in South Korea[28-30] and Yamato M in Japan[31-33], have pioneered innovations in esophageal stricture treatment. Their work spans endoscopic techniques, tissue engineering, and regenerative medicine, demonstrating the benefits of interdisciplinary collaboration. The diverse research focuses in the United States and Japan-ranging from Barrett's esophagus to ESD and tissue engineering-underscore regional differences in addressing esophageal strictures. These efforts collectively advance the understanding and management of this complex condition [18,34-37]. The top 10 most-cited references globally illustrate the diversity of the research landscape concerning esophageal stricture, encompassing various diagnostic and therapeutic techniques. These include methods for evaluation and treatment methods such as endoscopic techniques (*e.g.*, radiofrequency ablation), classification systems for specific diseases (*e.g.*, eosinophilic esophagitis), and advancements in tissue engineering and cell therapy. A noticeable divergence exists between the research focuses of the United States and Japan. Research in the United States has focused primarily on the evaluation and treatment of Barrett's esophagus and GERD[16], whereas Japan has emphasized ESD and tissue engineering therapies[18]. Endoscopic technology plays a crucial role in diagnosing and treating esophageal stricture. Endoscopic technology is pivotal in both diagnosing and treating esophageal stricture, and endoscopy-related research constitutes a substantial portion of the highly cited articles in both countries.

Treatment and research of esophageal stenosis

Esophageal stricture research addresses a variety of causes, including congenital anomalies, GERD, esophagitis, tuberculosis, and tumors, with a focus on prevention and treatment. This complexity arises from the multifactorial nature of the disease, which involves congenital defects, chronic inflammation, infections, and tumors. Congenital anomalies such as esophageal atresia and tracheoesophageal fistula often require early surgical intervention, but strictures may develop post-surgery, necessitating long-term monitoring. GERD, caused by acid reflux, is a leading cause of chronic esophageal inflammation, potentially resulting in stricture formation[38]. The global prevalence of GERD is estimated to be between 8% and 33%[39]. GERD is widespread in modern society, especially among young people, due to lifestyle changes, such as excessive intake of alcohol, coffee, chocolate, and high-fat foods or lying down immediately after meals, which can easily trigger GERD[40]. If severe GERD is not effectively treated over a long period, it may lead to esophageal stricture. Research has emphasized the effective management and treatment of GERD to prevent esophageal stricture, including the use of proton pump inhibitors and lifestyle changes to reduce stomach acid reflux[41]. Esophagitis, particularly inflammation of the esophageal tissue caused by corrosive chemicals or physical trauma, is another major cause of esophageal stricture[42,43]. Recurrent esophagitis can lead to fibrosis and stricture of the esophageal wall, which usually requires management through medication and endoscopic treatment methods[44]. Additionally, esophageal tuberculosis and esophageal tumors are essential causes of esophageal stricture, especially in developing countries. Esophageal strictures caused by tuberculosis require antituberculosis treatment and surgical intervention[45], whereas esophageal tumors typically require a combination of surgery, radiotherapy, and chemotherapy[46]. Given the diverse causes of esophageal stricture, treatment strategies must be comprehensive and tailored[47,48]. Common approaches include medication, endoscopic techniques, surgery, and stent placement. Medication, such as corticosteroids, is used for inflammatory causes. Endoscopic treatments such as balloon dilation and incision therapy have been shown to be effective in improving outcomes and reducing complications[49,50]. Surgical intervention is often necessary for severe cases, such as congenital defects or tumors, and multidisciplinary approaches enhance safety and efficacy[46]. In the past two decades, the use of esophageal stents has rapidly evolved from rigid plastic tubes to flexible self-expanding metal, plastic, and biodegradable stents. In the palliative treatment of malignant dysphagia, both self-expanding metal and plastic can quickly and effectively alleviate symptoms. Randomized controlled trials have shown that plastic stents present more

technical difficulties and late migration, making self-expanding metal more favored than plastic[51].

Esophageal stricture treatment methods are continuously evolving, with numerous new technologies and therapies being research. These include endoscopic drug injection, antifibrotic drugs, biodegradable stents, autologous tissue transplantation, and regenerative medicine. Endoscopic drug injection delivers targeted medication to the stricture site, alleviating inflammation and fibrosis, with corticosteroids commonly used to suppress inflammation and prevent further fibrosis[52,53]. Self-expanding stents combined with steroids improve outcomes by keeping the stricture open and releasing drugs to reduce fibrosis[54]. These stents can keep the esophageal stricture site open. Moreover, the continuous release of drugs can reduce collagen synthesis and alleviate fibrosis and scar formation, thus achieving prolonged therapeutic effects. Experimental studies have also shown that injecting autologous esophageal epithelial cell suspensions can promote re-epithelialization and reduce fibrosis, thereby decreasing the severity of esophageal strictures after ESD [55]. Further research is needed to confirm its future clinical use. Antifibrotic drugs play crucial roles in treating esophageal strictures. By inhibiting the formation of fibrous tissue, these drugs can effectively prevent the worsening of esophageal strictures, thereby reducing patient suffering and improving quality of life[56]. These drugs work through various mechanisms, such as inhibiting collagen synthesis, reducing local inflammatory responses, and preventing the excessive proliferation of fibroblasts. They typically include steroids, anti-inflammatory drugs, and specially designed antifibrotic medications[57]. Compared with metal stents, biodegradable stents are advantageous because they reduce long-term complications and reinterventions, offering safer and more effective treatments for refractory esophageal strictures[58]. Autologous tissue transplantation, in which the patient's tissue is used for repair, reduces the degree of rejection risk and enhances healing[59]. The use of acellular dermal matrix may also be as effective as autologous mucosal transplantation in preventing stricture formation after ESD. The core of this technique is to extract the required tissue from healthy parts of the patient's body and then transplant it to damaged or repair-needed areas[60]. Regenerative medicine, which uses stem cells and tissue engineering, aims to restore damaged esophageal tissue. Stem cells, which are capable of differentiating into various cell types, promote the growth of healthy esophageal tissue when transplanted [61]. Tissue engineering technologies, such as biological scaffolds, support cell attachment and growth[62]. Experiments have successfully constructed esophageal tissue *via* mesenchymal stem cells and scaffolds[63]. Biomaterials such as hydrogels have also shown promise in reducing stricture incidence after endoscopic procedures, promoting healing and reducing inflammation[64]. While these therapies are still in development, they offer hope for improving treatment outcomes and patient quality of life.

Limitations

Our bibliometric analysis relies solely on specific databases, which may lead to the omission of important research from other databases. Additionally, the coverage and inclusion criteria of different databases vary, potentially affecting the comprehensiveness and representativeness of the results. Research often covers specific periods, ignoring earlier or more recent research developments, which may result in a biased understanding of research trends. Bibliometric analysis relies mainly on quantitative indicators such as citation counts, which may not fully reflect the actual impact and quality of the research. For example, a high citation rate may be due to negative reviews or controversial content. Most databases prioritize the inclusion of English literature, which may lead to the underestimation or neglect of relevant research from non-English-speaking countries and regions.

CONCLUSION

With the advancement of more clinical studies and continuous technological improvements, the treatment of esophageal stricture will become more precise and personalized, resulting in more significant benefits to patients. The development of esophageal stricture research indicates that this field is vibrant and ever-expanding. Progress in regenerative medicine and tissue engineering is expected to achieve breakthroughs in the future, while the continuous development of endoscopic and pharmaceutical treatments ensures the improvement of patient care. Clinical trials and meta-analyses have strengthened evidence-based medicine, enhancing the reliability of treatment methods. Researchers consistently focus on patient safety and treatment efficacy, highlighting their comprehensive approach to addressing this complex medical challenge.

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FOOTNOTES

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CASE REPORT

Nonsurgical treatment of postoperative intestinal obstruction caused by heterotopic ossification of the mesentery: A case report

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Abstract

BACKGROUND

Among all forms of heterotopic ossification, heterotopic mesenteric ossification (HMO) is rare, with fewer than 100 reported cases to date. Postoperative early small bowel obstruction caused by HMO is even rarer, presenting extremely high surgical risks, the potential for multiple surgeries, and a poor prognosis. There have been no reported cases of conservative treatment for resolving such early postoperative obstruction.

CASE SUMMARY

A 57-year-old male presented with severe postoperative small bowel obstruction shortly after undergoing open radical resection for transverse colon cancer. Laparotomy revealed extensive adhesions in the proximal jejunum and mesentery, making it too difficult to relieve without injuring the small bowel. Additionally, multiple fixed nodules were found in the mesentery during the operation. Pathology confirmed the presence of heterotopic ossification. The patient was treated with methylprednisolone on postoperative day 1, which gradually relieved his symptoms.

CONCLUSION

Hormone therapy may have a potential role in treating small bowel obstruction caused by early HMO after operative intervention.

Key Words: Heterotopic mesenteric ossification; Hormone therapy; Bowel obstruction; Methylprednisolone; Surgery; Case report

Core Tip: In this case, we present a unique treatment approach for resolving early postoperative heterotopic ossification of mesentery-induced small bowel obstruction. There was difficulty dissecting the small bowel obstruction during the second surgery, thus we tried treatment with methylprednisolone, which gradually relieved the patient's bowel obstruction, thereby providing a new and effective strategy for early postoperative heterotopic ossification of the mesentery-induced small bowel obstruction and hypothesizing that early postoperative heterotopic ossification of the mesentery is a specific postoperative inflammatory response.

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INTRODUCTION

Heterotopic ossification refers to the formation of bone tissue in soft tissue where there is normally no bone tissue, which is an unusual pathological state. Heterotopic ossification was first discovered by the German doctor Riedel in 1883 and is commonly found in the limbs, especially the elbow joint[1]. Heterotopic mesenteric ossification (HMO) is extremely rare. In 1983, Hansen *et al*[2] first reported HMO. However, to date, fewer than 100 cases have been reported. Here, we report the case of a patient with colorectal cancer who underwent radical resection and developed HMO within a short period of time, accompanied by severe intraabdominal obstruction. Despite our inability to resolve the obstruction during surgery, treatment with methylprednisolone gradually relieved the patient's obstruction and prevented further progression of HMO.

CASE PRESENTATION

Chief complaints

A 57-year-old Han Chinese male underwent open radical surgery for transverse colon cancer. Postoperative abdominal distension progressively worsened, and severe abdominal pain developed on the 14th day after surgery, which was unbearable.

History of present illness

The patient underwent open radical resection for transverse colon cancer. On the fifth day after surgery, the patient experienced persistent abdominal distension and was unable to pass gas or stool. We employed non-operative managements, including nasogastric decompression, fluid resuscitation, and correction of electrolyte abnormalities. On the 13th postoperative day, the patient's abdominal distension intensified. We suspected that intestinal obstruction might be due to stenosis at the anastomotic site. Colonoscopy revealed that the anastomotic site was unobstructed. Consequently, we further identified intestinal obstruction in multiple segments of the small intestine through computed tomography (CT). On the 14th day, the patient's abdominal distension worsened, and the patient experienced unbearable abdominal pain. Intestinal obstruction after radical resection of transverse colon cancer was considered.

History of past illness

The patient had a 15-year history of hypertension, which was controlled. He was diagnosed with cerebral hemorrhage in 2011 and underwent left inguinal hernia repair 8 years ago.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

Physical examination revealed abdominal distention, abnormal bowel sounds, tenderness in the abdomen, and no Blumberg's sign.

Laboratory examinations

Alkaline phosphatase activity was elevated, and other indicators were normal.

Imaging examinations

Colonoscopy revealed that the anastomosis was unobstructed without stenosis, but the mucosa of the proximal small intestine was markedly edematous, making it impossible for the colonoscope to pass through. A CT scan revealed dilation of the small bowel (Figure 1A and B), but no other abnormalities were observed.

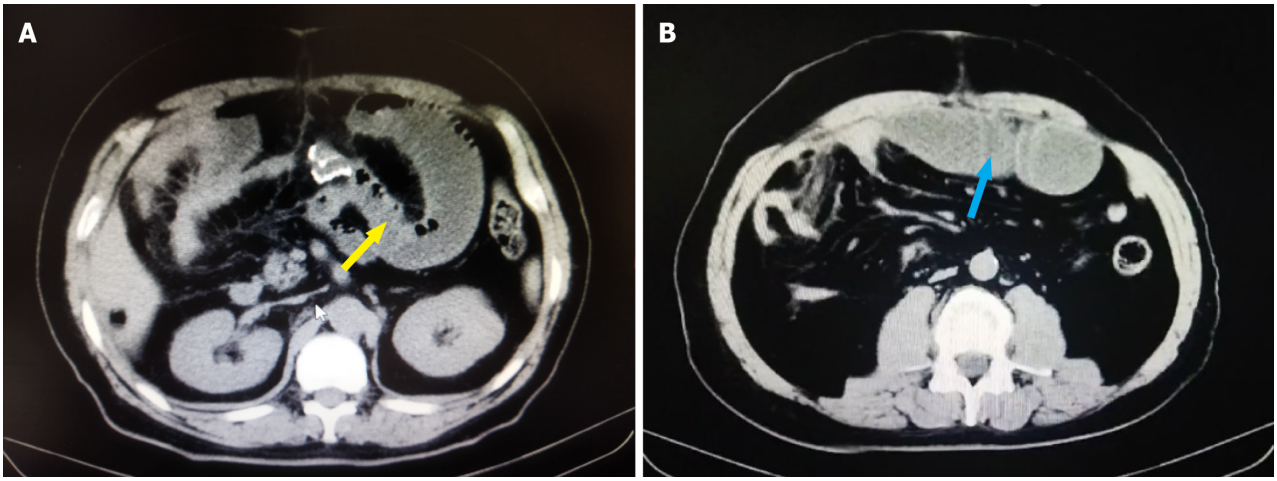

Figure 1 Abdominal computed tomography revealed intestinal obstruction of the patient after abdominal surgery. A: The yellow arrow indicated the patient's intestinal obstruction at the right renal hilus level; B: The blue arrow indicated the patient's intestinal obstruction at the umbilical level.

FINAL DIAGNOSIS

The final diagnosis was intestinal obstruction.

TREATMENT

Laparotomy revealed segmental intestinal obstruction in multiple segments, with extensive and tight adhesions of the proximal jejunum and mesentery near the flexure of the ligament of Treitz, approximately 35 cm from the ligament. The original colonic flexure and the original site of the hepatic flexure were also extensively adhered (Figure 2A). The entire small intestine was adhered together like a cake, and the adhesion strength was significantly greater than that of normal abdominal adhesions 14 days after surgery. There was no free small intestine longer than 10 cm in the abdominal cavity, which prevented us from identifying the proximal and distal ends. Thus, enterostomy could not be performed. Attempts at blunt and sharp dissection failed to completely resolve the intestinal obstruction. Even if the surgeon avoided the use of energy-based cutting, carefully dissecting the patient with scissors can still easily damage the small intestine. Additionally, multiple fixed nodules, which were not present in the previous operation, were found in the mesentery during the operation (Figure 2B). If these fibroses and adhesions were forcibly dissected, there would be a high risk of small intestinal fistula development, so the abdomen was closed. After pathological analysis of mesenteric nodules, patchy new cartilage, bone tissue, and fibrous tissue were found to have proliferated (Figure 3A and B).

Postoperative care included fasting, placement of an intestinal obstruction set, suppression of digestive fluid secretion with octreotide, and nutritional support. The intestinal obstruction set was difficult to place through the ligament of Treitz. Methylprednisolone was given for anti-inflammatory and symptomatic treatment for one week, with an initial dose of 40 mg per day followed by 40 mg twice a day for the next two days and then 40 mg per day until the seventh day, followed by discontinuation on the eighth day. The patient was monitored closely for complications such as stress ulcers and electrolyte imbalances.

OUTCOME AND FOLLOW-UP

The intestinal obstruction gradually improved after one week of hormone therapy (Figure 4A), and the patient was discharged from the hospital on the 25th day after the second surgery. At the eight-month follow-up visit, the patient reported no discomfort. CT imaging revealed no significant abnormalities (Figure 4B).

DISCUSSION

The occurrence of HMO is the result of specific signaling molecules in the peritoneal cavity that induce mesenchymal stem cell osteogenesis, and abdominal trauma and surgery seem to be the triggering factors for this process[3,4]. Another explanation is that trauma and surgery lead to the transplantation of bone tissue to the mesentery[5]. A review of the literature (Supplementary Table 1) revealed that most of the reported cases of HMO were found in males (57/64, 89.06%), with a median age of 51.5 years (range 21-88 years), and are closely related to a history of abdominal trauma and surgery (52/58, 89.66%). The remaining cases were spontaneous HMO[6]. HMO primarily occurs in the small intestinal mesentery (50/64, 78.13%), and the symptoms mainly manifest as small intestinal obstruction (32/58, 55.17%)[7] and enterocu-

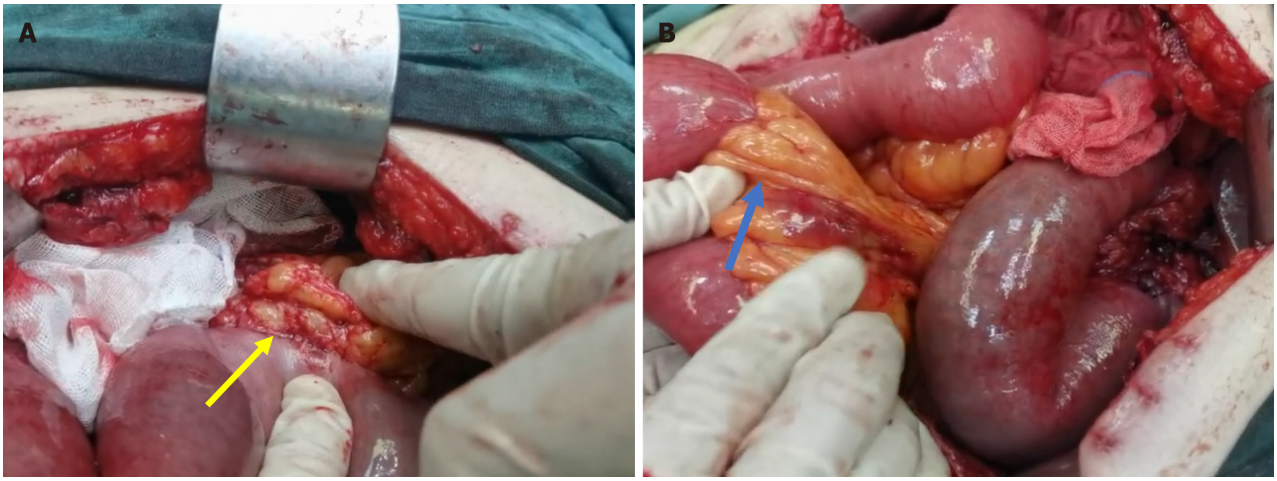

Figure 2 Intraoperative observations may reveal the presence of abdominal adhesions and mesenteric nodules. A: The yellow arrow indicated a tight adhesion between the mesentery and the small intestine; B: Blue arrow indicated multiple hard nodules in the mesentery.

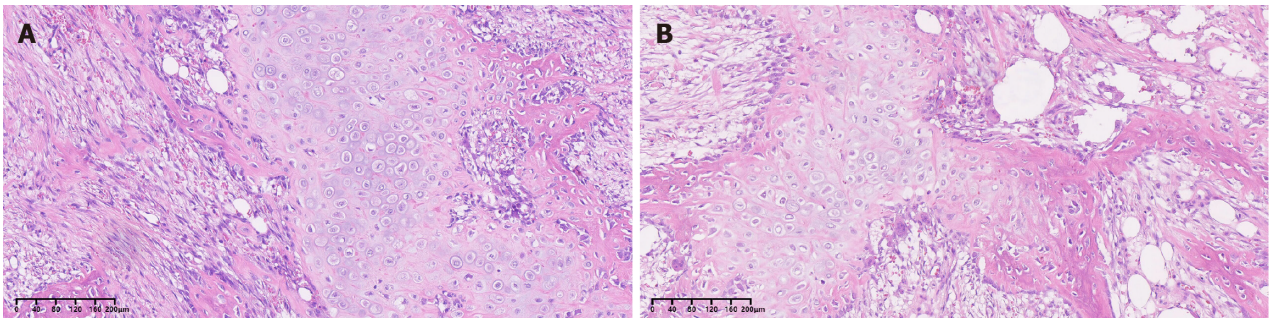

Figure 3 Pathological findings of surgical specimens. A and B: Representative hematoxylin and eosin images of mesenteric nodules. Hematoxylin and eosin images showed heterotopic ossification and new bone formation. Black color scale bars: 200μm. The immunohistochemical staining results were as follows: CD68 (+), smooth muscle actin (+), CD34 (+), β-catenin (cytoplasmic+), Ki-67 (+20%), and deamin (-).

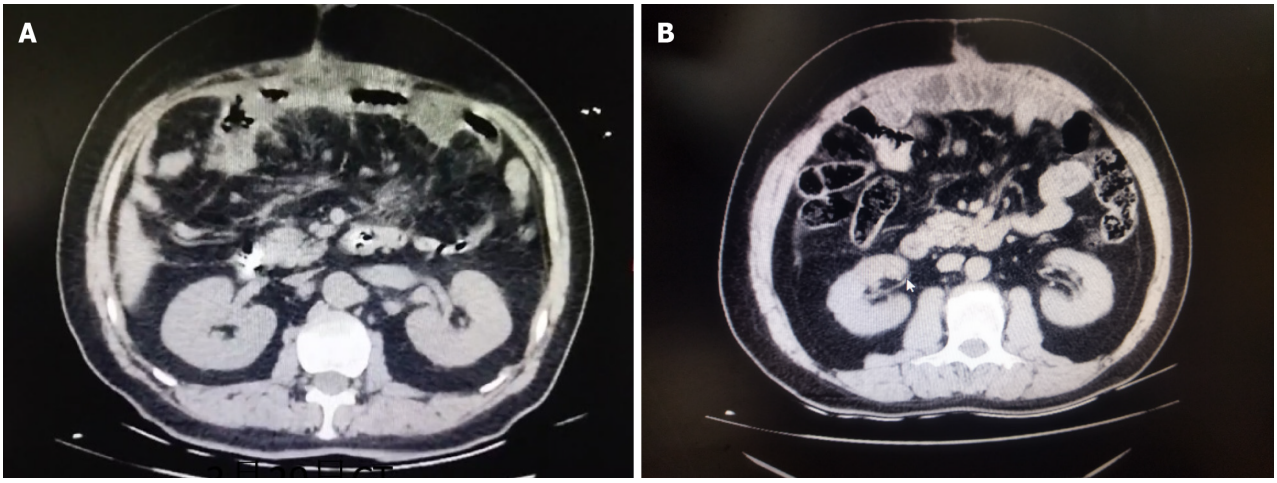

Figure 4 Abdominal computed tomography showed a significant alleviation of intestinal obstruction following methylprednisolone treatment. A: After 1 week of methylprednisolone treatment, there was a marked reduction in the intestinal obstruction; B: 8 months after methylprednisolone treatment.

Table 1 Summary of the previously reported cases of early postoperative heterotopic omental ossification

Year	Age	Sex	Primary disease/operation	Clinical history	Onset	Site	Therapy	Outcome
1983	55	Male	Ulcerative colitis/surgery	SBO	2 weeks	M	OP	Relapse
2000	25	Male	Fire-gun injury/surgery	SBO	2 weeks	M	OP	Relapse
2005	74	Male	Intestinal obstruction/surgery	SBO	10 days	M, O	OP	Death
2010	50	Male	Morbid obesity/surgery	Fistula/SBO	12 days	M, O	OP	Relapse
2011	39	Male	Cancer/surgery	SBO	2 weeks	O	OP	Recovery
2014	88	Male	Abdominal aortic aneurysm/surgery	SBO	2 weeks	M	OP + NSAIDs	Recovery
2018	72	Male	Cancer/surgery	SBO	SW	M	OP	Death

SBO: Small bowel obstruction; SW: Several weeks; M: Mesentery; O: Omentum; OP: Operation; NSAIDs: Nonsteroidal anti-inflammatory drugs.

taneous fistula (6/58, 10.34%)[8]. There are no specific laboratory findings associated with HMO, and only alkaline phosphatase may be elevated[9], which may be related to the increased activity of osteoblasts and the need for more case support. The unique feature of this case was the rapid formation of bone tissue, with bone formation occurring within 14 days, which may have been due to insufficient deposition of calcium salts, and the CT scan did not show a high-density image. Second, HMO is accompanied by a strong inflammatory reaction in the abdominal cavity, with extensive adhesions forming between the small intestine, mesentery, and peritoneum. Finally, after hormonal therapy, there was gradual relief of the intestinal obstruction that could not be relieved by mechanical dissection, which is encouraging. The patient's stool gradually transformed from a clay-colored consistency to a normal appearance (Supplementary Figure 1). Most gastrointestinal surgeons might not encounter such postoperative complications during their career. However, they should remain vigilant in preventing inflammatory intestinal obstruction caused by early postoperative HMO. Although only 7 cases of early postoperative HMO have been reported, they share common features: Rapid onset, extensive adhesions leading to difficulty in dissection, small intestinal obstructions, thick mesenteries, and hard fibrous osteoid tissue forming on the mesentery within 1 month after surgery. In such instances, there is a significantly elevated surgical risk owing to the inability to dissect inflammatory adhesions without causing damage to the small intestine. This increases the likelihood of multiple operations, reduces patient tolerance for such procedures, and leads to a poor prognosis. Only one of the seven patients recovered after intestinal adhesion dissection (Table 1)[10], and one patient recovered after the removal of 240 cm of the obstructed small intestine in addition to receiving nonsteroidal anti-inflammatory drug treatment[11]. Two patients died from postoperative complications resulting from multiple surgeries[12,13]. Moreover, three patients experienced recurrence following adhesiolysis or intestinal resection, necessitating multiple subsequent surgeries[2,14,15].

Ectopic ossification may represent a nonspecific inflammatory response. Methylprednisolone has been shown to inhibit inflammation resulting from both infectious and noninfectious factors by preventing inflammatory mediators from reacting and inhibiting complement involvement in the inflammatory response while also mitigating tissue damage repair following inflammation. In the advanced stage of inflammation, it can also suppress the vitality of fibroblasts, decrease the soluble collagen components in tissues, and minimize adhesion and scar formation. Although there are no documented successful cases thus far, hormonal therapy has emerged as an option that should potentially be pursued. Without such intervention, patients may face imminent mortality due to the inability to sustain parenteral nutrition or progressive energy failure. Fortunately, we successfully treated these inflammatory bowel obstructions with methylprednisolone, avoiding the risk of multiple surgeries, preserving the patient's entire small intestine, and saving the patient's life. The patient has been discharged from the hospital for more than eight months, and follow-up examinations revealed that the patient is in excellent health. Surgeons should consider this approach as a final attempt when confronted with similar challenges subsequent to unsuccessful surgical intervention (Video 1).

CONCLUSION

In conclusion, early HMO may be accompanied by severe intra-abdominal inflammatory reactions, leading to intestinal obstruction. Our therapeutic approach provides a new treatment possibility for intestinal obstruction caused by early postoperative HMO, but more clinical cases are still needed for confirmation.

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FOOTNOTES

Author contributions: Chen JT collected data and wrote the manuscript; Guo SQ and Huang JS contributed to the literature search; Wang YG and Li YP designed the study; and all the authors have read and approved the final manuscript.

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CASE REPORT

Lung metastasis following temporary discontinuation of lenvatinib and tislelizumab in hepatocellular carcinoma: A case report

Chen-Dong Wang, Run-Dong Liu, Ming-Jie Liu, Jia Song

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a prevalent malignancy in China, primarily diagnosed at advanced stages, which limits treatment options and increases mortality rates. Conversion therapy, which includes systemic and locoregional treatments, aims to render unresectable tumors resectable. Nonetheless, research is scant on the risks of disease progression during the temporary cessation of targeted drugs and immune checkpoint inhibitors before surgery.

CASE SUMMARY

This report describes a 58-year-old male with HCC who developed lung metastases following the discontinuation of lenvatinib and tislelizumab, revealing the necessity for further investigation into the management of HCC patients during the perioperative period, particularly concerning the timing and duration of targeted therapy and immunotherapy.

CONCLUSION

Our study highlights the complex challenges in managing advanced HCC and emphasizes the critical need for ongoing research to refine treatment strategies and improve patient outcomes.

Key Words: Hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; Lenvatinib; Tislelizumab; Conversion therapy; Case report

Core Tip: In recent years, targeted therapies, immunotherapies with immune checkpoint inhibitors, and localized interventions have effectively managed advanced or non-resectable hepatocellular carcinoma (HCC). Despite these advances, few studies have addressed the crucial need for management strategies during the perioperative period for patients with HCC. To our knowledge, this is the first report to illuminate the potential risk of disease progression and lung metastasis after the temporary cessation of targeted therapy with lenvatinib and immunotherapy with tislelizumab. This finding reveals the importance of refining treatment protocols to reduce the risks of recurrence and metastasis.

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INTRODUCTION

Liver cancer is the fourth most common malignant tumor in China[1], with hepatocellular carcinoma (HCC) constituting over 80% of primary liver cancer cases[2]. A comprehensive review of the treatment landscape for HCC in China indicates that a majority of patients are diagnosed at intermediate to advanced stages [China Liver Cancer stage IIb, IIIa, and IIIb, encompassing a proportion of patients with Barcelona Clinic Liver Cancer (BCLC) stage B and all patients with BCLC stage C][3]. This late-stage diagnosis typically precludes surgical options, contributing significantly to the high mortality rates associated with HCC.

In this context, the advent of conversion therapy has transformed the treatment paradigm for patients with intermediate or advanced HCC. Conversion therapy aims to render unresectable HCC resectable, thereby facilitating surgical resection[4]. This approach includes a combination of systemic and locoregional treatments, such as transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and radiotherapy. Systemic therapies, particularly those combining anti-angiogenic drugs with immunotherapy, have demonstrated an objective response rate of approximately 30%[5], with associated promising median survival times extending up to 20 months[6-8]. Locoregional treatments, such as TACE and HAIC, have also proven effective in conversion therapy for unresectable HCC, with HAIC showing greater efficacy than TACE[9].

Despite these advancements, a critical gap persists in our understanding of the risks associated with discontinuing targeted drugs and immune checkpoint inhibitors (ICIs) during the pre-surgical waiting period. We present the first case of lung metastasis occurring during a cessation period of lenvatinib, which was planned prior to surgical resection. This case reveals the urgent need for further research into optimal management strategies during this critical phase of treatment, aiming to minimize the risks of disease progression and metastasis while patients await surgery.

CASE PRESENTATION

Chief complaints

A 58-year-old man was referred to our hospital due to being diagnosed with chronic hepatitis type B and HCC in October 2023.

History of present illness

The patient was incidentally diagnosed with chronic hepatitis B virus infection during a routine examination. Subsequent ultrasonography at a local hospital revealed a large tumor at the transition zone between the left and right lobes of the liver.

History of past illness

The patient had no significant medical history prior to this diagnosis.

Personal and family history

The patient denied any familial history of HCC.

Physical examination

Physical examination revealed no symptoms of jaundice, vascular spiders, palmar erythema, or other abnormal signs.

Laboratory examinations

Initial laboratory tests showed the following results: Alanine aminotransferase 28 U/L, aspartate aminotransferase 78 U/L, total bilirubin albumin 16.0 μmol/L, and prothrombin time 12.6 s. Tumor biomarkers were notably elevated with alpha-fetoprotein (AFP) at 60500 ng/mL and Prothrombin Induced by Vitamin K Absence or Antagonism Type II (PIVKA-II) at 23099.79 mAu/mL. Quantitative HBV-DNA testing indicated a viral load of 1.11×10^2 IU/mL.

Imaging examinations

During the first admission, magnetic resonance imaging showed a large mass located at the transition zone between the left and right lobes of the liver, measuring approximately 14 cm (Figure 1).

FINAL DIAGNOSIS

The conclusive diagnosis for the case was HCC with no pulmonary metastasis (Figure 2).

TREATMENT

Considering the extensive tumor burden, surgical resection was deemed potentially unsuitable for the patient. Consequently, a multimodal therapeutic approach was employed. The patient received HAIC followed by treatment with tyrosine kinase inhibitors (TKIs) and ICIs. The HAIC regimen included oxaliplatin at a dose of 85 mg/m^2, leucovorin at 400 mg/m^2, and intra-arterial 5-fluorouracil at 400 mg/m^2 on day 1.

This was followed by a repeated infusion of 5-fluorouracil at a dose of 2400 mg/m^2 on days 2–3, with a three-week interval between each treatment cycle. The treatment strategy involved evaluating the patient after every two cycles of HAIC. Initially, on October 30, 2023, the FOLFOX regimen was first administered to the patient. Following nearly three days of infusion chemotherapy, the patient was proposed to commence daily lenvatinib (8 mg) and intravenous tislelizumab 200 mg, an anti-PD-1 monoclonal antibody, every three weeks (Figure 3). Additionally, considering the HBV burden, the patient was prescribed daily antiviral therapy with tenofovir amibufenamide (25 mg). The primary adverse reactions during HAIC treatment included abdominal pain and nausea.

Since February 4, 2024, after four cycles of the planned HAIC, TKIs, and ICIs, TACE was integrated into the adjuvant therapy regimen instead of HAIC to further enhance treatment efficacy. Concurrently, lenvatinib and tislelizumab were temporarily halted in preparation for the upcoming surgical intervention.

OUTCOME AND FOLLOW-UP

After four cycles of therapy, a response evaluation was conducted. Notably, there was a decrease in PIVKA-II levels to 65.58 mAu/mL and AFP levels to 288.70 ng/mL (refer to Figure 4). Radiologic imaging showed partial response (PR) in the lesions (Figure 2A). Based on these improvements in tumor biomarkers and the modified Response Evaluation Criteria in Solid Tumors criteria, the patient was considered potentially eligible for surgical resection due to well-restricted tumor activity. Since February 04, 2024, TACE replaced HAIC in the adjuvant therapy regimen to further enhance treatment effectiveness. Concurrently, lenvatinib and tislelizumab were temporarily suspended in preparation for surgery.

On February 21, 2024, the patient returned to Tongji Hospital for surgical resection. Upon arrival, a comprehensive preoperative assessment was initiated to evaluate his suitability for surgery. Unfortunately, computed tomography imaging revealed multiple metastatic sites in the lungs (Figure 1B), necessitating the cancellation of the planned operation.

DISCUSSION

As previously noted, most HCC patients are diagnosed at intermediate or advanced stages[3], where direct surgical intervention may offer better outcomes than non-surgical approaches in a small, carefully selected subset of patients[10]. However, the high recurrence rate post-surgery indicates that surgery often fails to provide a curative outcome for late-stage patients[11]. Meanwhile, advancements in systemic and locoregional therapies have improved response rates among those with unresectable or advanced HCC[5]. These therapies have enabled tumor downstaging to the point where surgical resection becomes feasible, a strategy known as conversion therapy.

Recent systemic therapies combining TKIs and ICIs have shown favorable effects. Zhu *et al*[12] reported that among 63 patients initially diagnosed with unresectable liver cancer, 15.9% achieved conversion to resection through combined PD-1 inhibitors and TKI therapy. Disappointing results from monotherapy have steered the trend towards integrating local and systemic therapies in managing advanced HCC. In a randomized controlled trial comparing the efficacy of HAIC and sorafenib *vs* sorafenib alone in patients with HCC and portal vein invasion, 12.8% of patients in the combination therapy group experienced downstaging post-treatment and underwent radical surgical resection[13]. This reveals the potential of

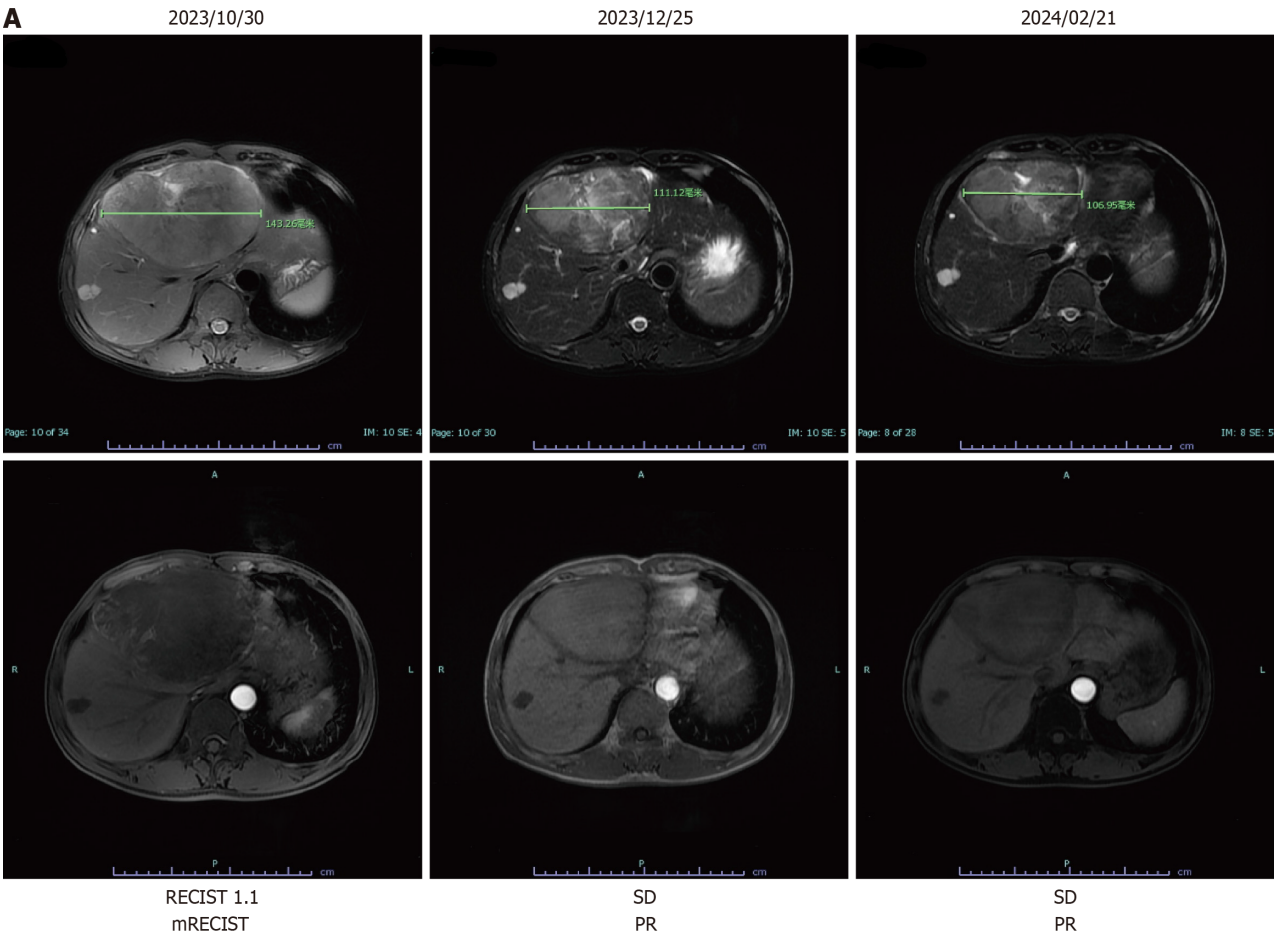

Figure 1 Imaging of liver and lung during different periods. A: Radiologic assessments showed a partial response based on the modified Response

Evaluation Criteria in Solid Tumors criteria; B: Computed tomography imaging examination indicated multiple metastatic sites in the lung on February 23, 2024. mRECIST: Modified Response Evaluation Criteria in Solid Tumors; PR: Partial response; SD: Stable disease.

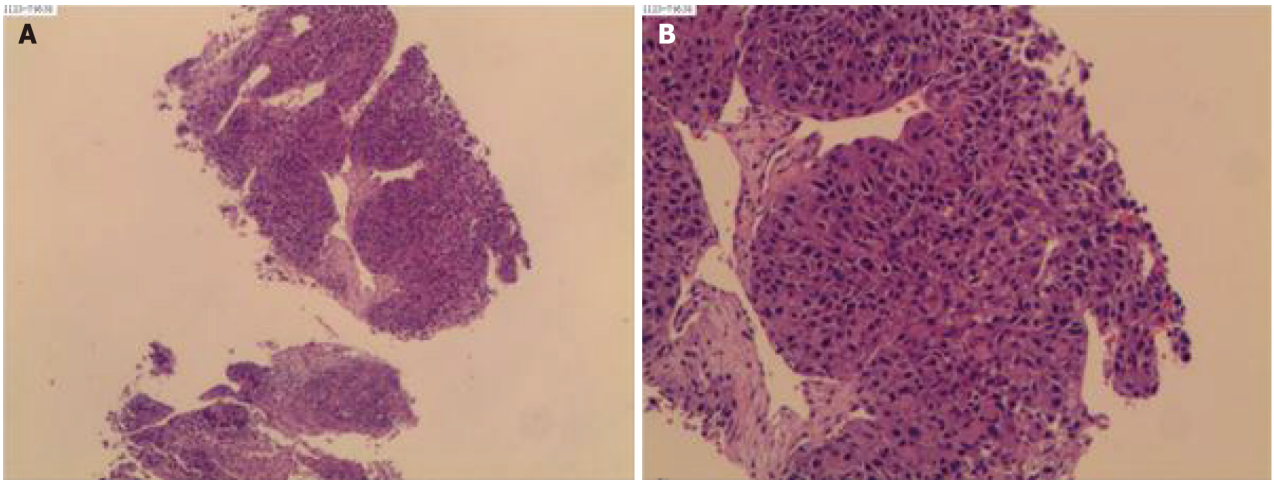

Figure 2 Liver Biopsy. The outcome confirmed the diagnosis of hepatocellular carcinoma (poor differentiation) on December 06, 2023. A and B: The microscopic view of the liver biopsy.

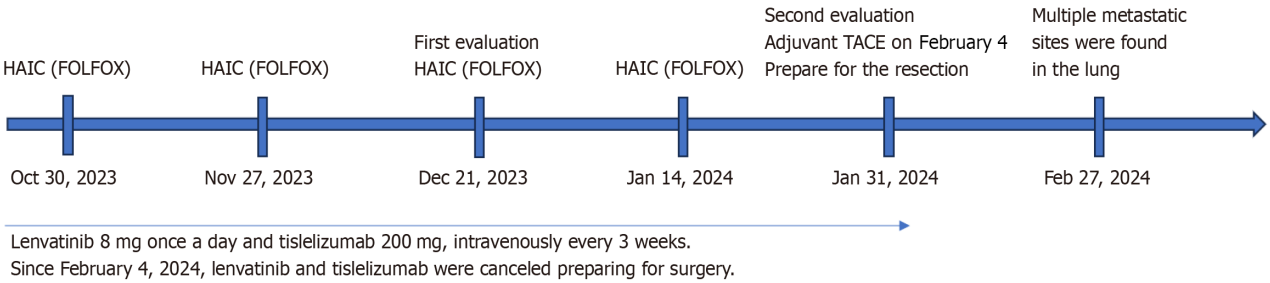

Figure 3 Timeline of treatment. After four courses of the hepatic arterial infusion chemotherapy regimen, lenvatinib and tislelizumab were canceled, preparing for surgery. Multiple metastatic sites were found in the lung on February 27, 2024. HAIC: Hepatic arterial infusion chemotherapy; TACE: Transcatheter arterial chemoembolization.

combining HAIC (FOLFOX) with TKIs and PD-1 inhibitors to achieve superior tumor shrinkage and extend survival, making this combination a promising approach for improving outcomes in HCC management.

In this case study, we report on a patient where conversion therapy nearly succeeded using a combined treatment regimen of HAIC with FOLFOX, lenvatinib, and tislelizumab. While this approach effectively restricted tumor growth, lung metastasis unexpectedly developed after the cessation of lenvatinib and tislelizumab in preparation for radical surgery. Recent findings suggest a strong correlation between the duration of targeted therapy in melanoma and reduced risk of disease progression following drug discontinuation[14]. However, the relationship between cessation of targeted therapies and the development of new metastatic sites in HCC remains unclear. Lung metastasis might be part of the natural progression of HCC. This case highlights the urgent need for a revised management strategy that considers the timing of drug discontinuation and addresses the risk of recurrence or disease progression. Currently, there is no consensus on the optimal timing for surgical intervention in patients with advanced HCC that would prevent metastasis and manage primary tumor progression effectively.

CONCLUSION

In conclusion, our case report of a 58-year-old male with HCC who developed lung metastases after the temporary discontinuation of lenvatinib and tislelizumab underscores the complexities in managing advanced HCC. It highlights the challenges in managing advanced HCC and emphasizes the need for ongoing research to optimize treatment strategies and improve patient outcomes.

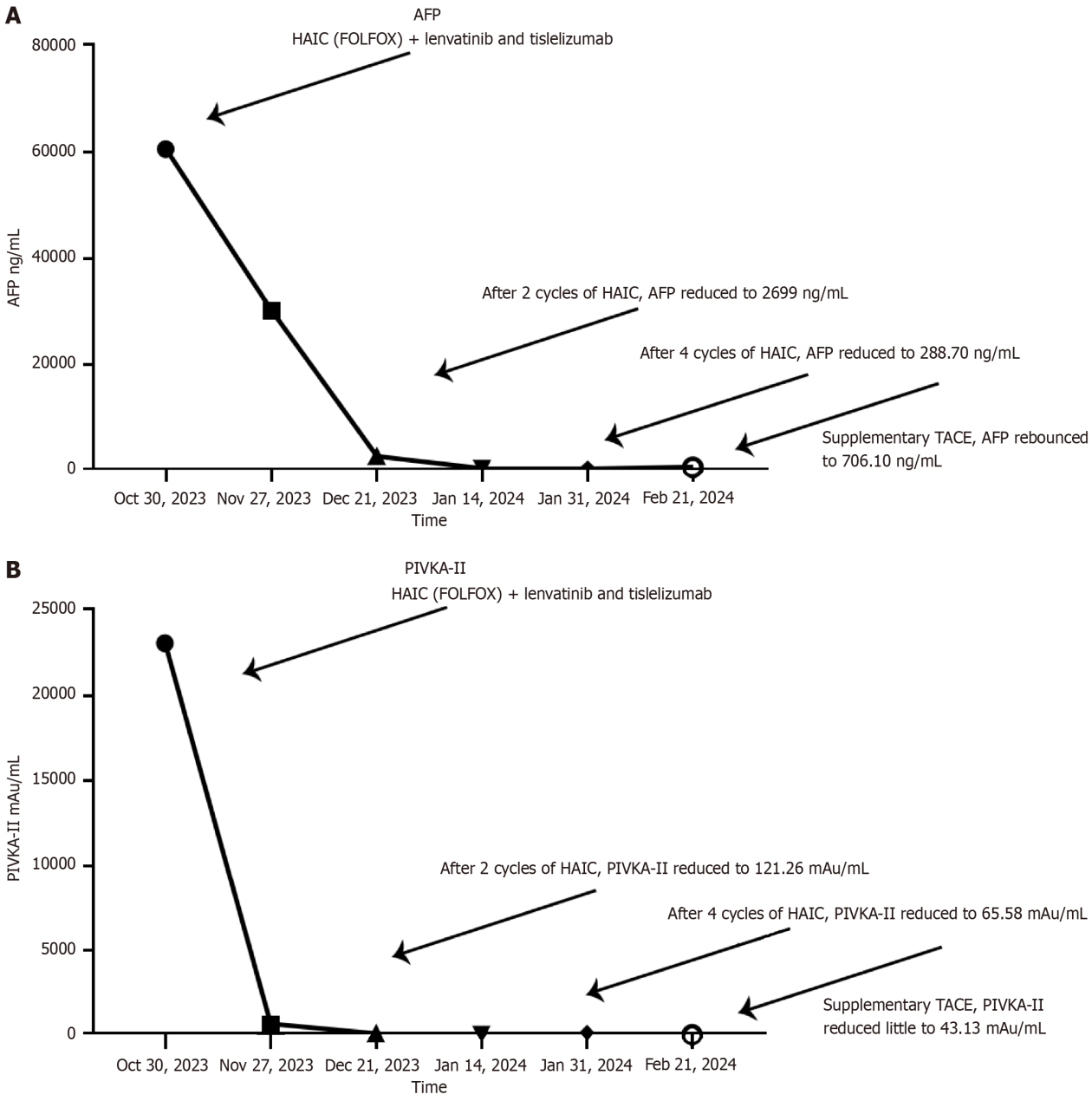

Figure 4 Trends of tumor markers during the treatment. A: Alpha-fetoprotein levels of different periods, drastic decrease could be observed during the combined therapy, while a decrease was observed after supplementary transcatheter arterial chemoembolization on February 4, 2024, replacing hepatic arterial infusion chemotherapy with lenvatinib and tislelizumab; B: Prothrombin Induced by Vitamin K Absence or Antagonism Type II levels of different periods, continuous decline was observed. HAIC: Hepatic arterial infusion chemotherapy; TACE: Transcatheter arterial chemoembolization; AFP: Alpha-fetoprotein; PIVKA-II: Prothrombin Induced by Vitamin K Absence or Antagonism Type II.

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FOOTNOTES

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CASE REPORT

Laparoscopic microwave ablation for giant cavernous hemangioma coexistent with diffuse hepatic hemangiomatosis: Two case reports

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Abstract

BACKGROUND

Hepatic hemangioma represents the most common benign primary hepatic neoplasm. Although most such tumors are small and asymptomatic, giant cavernous hemangioma (GCH) is frequently symptomatic, and needs intervention. Moreover, diffuse hepatic hemangiomatosis (DHH) is not rare in the liver parenchyma adjacent to a GCH. The management strategy for hepatic hemangiomas can differ depending on the presence of associated hemangiomatosis and the amount and distribution of the residual hepatic parenchyma.

CASE SUMMARY

Herein, we report two patients with GCH coexistent with DHH successfully treated by laparoscopic microwave ablation. The two GCHs were ablated completely and the ablated zone atrophied obviously in imaging follow-ups after ablation. Surprisingly, there was a trend toward gradual reduction and diminishment of DHH.

CONCLUSION

Thermal ablation treatment might be an effective and less invasive treatment for GCH coexistent with DHH around the hemangioma.

Key Words: Giant cavernous hemangioma; Diffuse hepatic hemangiomatosis; Management; Microwave; Thermal ablation; Case report

Core Tip: Hepatic hemangiomas are the most common benign liver tumors, with giant cavernous hemangioma (GCH) often requiring intervention. This report discusses two patients with GCH coexistent with diffuse hepatic hemangiomatosis (DHH), treated successfully with laparoscopic microwave ablation. Both GCHs were completely ablated, showing significant atrophy on follow-up imaging. Notably, there was also a gradual reduction in DHH. These findings suggest that thermal ablation may be an effective and minimally invasive option for managing GCH coexistent with DHH.

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INTRODUCTION

Hepatic hemangioma is the most frequently encountered solid benign liver neoplasm, with an incidence of 3% to 20% in the general population[1]. Giant cavernous hemangioma (GCH) is defined as being ≥ 5 cm and warranting therapy when it leads to continuous growth in clinical symptoms or the risk of complications[2]. Diffuse hepatic hemangiomatosis (DHH) is an uncommon disease of undetermined etiology characterized by numerous hemangiomas infiltrating and replacing the liver parenchyma[3,4]. In contrast to GCH, which presents with smooth, well-defined margins and typical imaging characteristics, DHH appears as a poorly defined lesion[5]. Isolated DHH without extrahepatic involvement is exceedingly rare in adults.

However, hemangiomatosis is frequently occurs in the liver parenchyma adjacent to a GCH[5]. The approach to managing hepatic hemangiomas varies based on the presence of associated hemangiomatosis and the extent and location of the remaining hepatic parenchyma. Surgical candidates must be selected with caution to mitigate complications, including excessive intraoperative blood loss and the risk of postoperative liver failure resulting from overestimation of functional residual liver volume due to unrecognized involvement by hemangiomatosis. Recently, thermal ablation treatment using radiofrequency (RF) ablation or microwave (MW) ablation has been investigated as a less invasive treatment for hepatic hemangioma, which has shown favorable outcomes[6,7]. However, thermal ablation has not been described in the published papers of hepatic hemangioma coexistent with DHH. We herein present two cases with GCH coexistent with DHH around the hemangioma that were treated successfully by laparoscopic MW ablation.

CASE PRESENTATION

Chief complaints

Case 1: In September 2022, a 63-year-old female was admitted to the hospital due to abdominal discomfort.

Case 2: In January 2024, a 54-year-old female was admitted to the hospital because regular follow-up images showed an enlarging hepatic hemangioma over the past 5 years.

History of present illness

Case 1: A hepatic hemangioma and multiple hepatic nodules were incidentally identified during a routine health check *via* abdominal ultrasound (US).

Case 2: No other specific discomfort was described.

History of past illness

Case 1: The patient had a documented history of hypertension.

Case 2: The patient had no previous abnormalities.

Personal and family history

No significant personal or family history was reported by both patients.

Physical examination

The physical examination findings of case 1 and case 2 were within normal limits.

Laboratory examinations

Laboratory tests revealed no abnormalities for both patients.

Imaging examinations

Case 1: A contrast-enhanced computed tomography (CT) scan demonstrated peripheral enhancement of the GCH (7.4 cm × 9.9 cm) and heterogeneous enhancement of the adjacent liver parenchyma affected by hemangiomatous lesions (Figure 1A-D).

Case 2: Contrast-enhanced CT demonstrated a GCH (10.7 cm × 8.2 cm) and multiple small hemangiomatous lesions adjacent to the hemangioma in the liver (Figure 2A and B).

FINAL DIAGNOSIS

Based on imaging findings and clinical features, both patients in the study were diagnosed with GCH coexistent with DHH.

TREATMENT

Case 1

Following multidisciplinary team discussions, laparoscopic MW ablation was planned and executed to target the hemangioma. Two hepatobiliary surgeons, each with over a decade of experience in percutaneous and laparoscopic image-guided MW ablation of giant hemangiomas, performed the procedures (Figure 1E-H). Tumor coagulation was achieved using an ECO-100Al8 internally cooled MW antenna and a water-cooled MW ablation system (Yigao Medical, Nanjing, China), with the power output set at 150 W and a frequency of 2450 MHz. Details of the MW ablation process have been previously described[1]. Intraoperative US monitored tissue responses, with hyperechoic areas indicating adequately ablated tissue due to gas release from heating. DHH lesions were left intact to preserve as much normal liver parenchyma as possible. The ablation procedure lasted 56 minutes, with a total operative time of 125 minutes, including 20 sessions of ablations at different tumor sites. Intraoperative blood loss, quantified through drained blood, was measured at 10 mL.

Case 2

Two hepatobiliary surgeons, each with over a decade of experience in percutaneous and laparoscopic image-guided MW ablation of giant hemangiomas, performed the procedures as previously described (Figure 2C-F). In the operative field, multiple small hemorrhagic blood-filled honeycomb areas from 2-3 mm up to 3 cm in diameter were scattered adjacent to the GCH throughout the entire left lobe (Figure 2D). To further obtain a definitive diagnosis, a liver biopsy was conducted from the left hepatic lobe. The ablation procedure lasted 37 minutes, with a total operative time of 165 minutes, including 5 sessions of ablations at different tumor sites. Intraoperative blood loss was measured at 20 mL. Histological findings of the resected liver tissue revealed that the large majority of the portal tracts and the central veins showed expansion due to the formation of micro-angiomas along with dilatation of the native vessels. Micro-angiomatous lesions were characterized by irregular-shaped dilated vascular channels arranged along with sinusoidal dilatation, some accompanied by tumor-like proliferation and red blood cell siltation seen in the lumen, and the stroma was hyperplastic fibrous tissue. The lesion was lined with flat endothelial cells without cellular atypia. This lesion was diagnosed as hemangiomatosis (Figure 2G and H).

OUTCOME AND FOLLOW-UP

Case 1

The patient was discharged on postoperative day 3 without significant complications, such as intrahepatic hematoma, and was in good health at the latest follow-up. Three months and 18 months after ablation, contrast-enhanced CT scans showed that the GCH was completely ablated and remarkably smaller. Moreover, a reduction in the size of DHH was noted (Figure 1I-P). No recurrence or delayed complications were identified, and the patient's subjective health status and quality of life were assessed as good to excellent at the final follow-up.

Case 2

The patient was discharged on postoperative day 5 without significant complications, such as intrahepatic hematoma, and was in good health at the latest follow-up. Four months after ablation, contrast-enhanced CT scans showed that the hepatic hemangioma was completely ablated and remarkably smaller. Moreover, a reduction in the size of DHH was noted too (Figure 2I and J). Subsequently, we will continue to monitor the patient's follow-up one year after ablation. No recurrence or delayed complications were identified, and the patient's subjective health status and quality of life were assessed as good to excellent at the final follow-up.

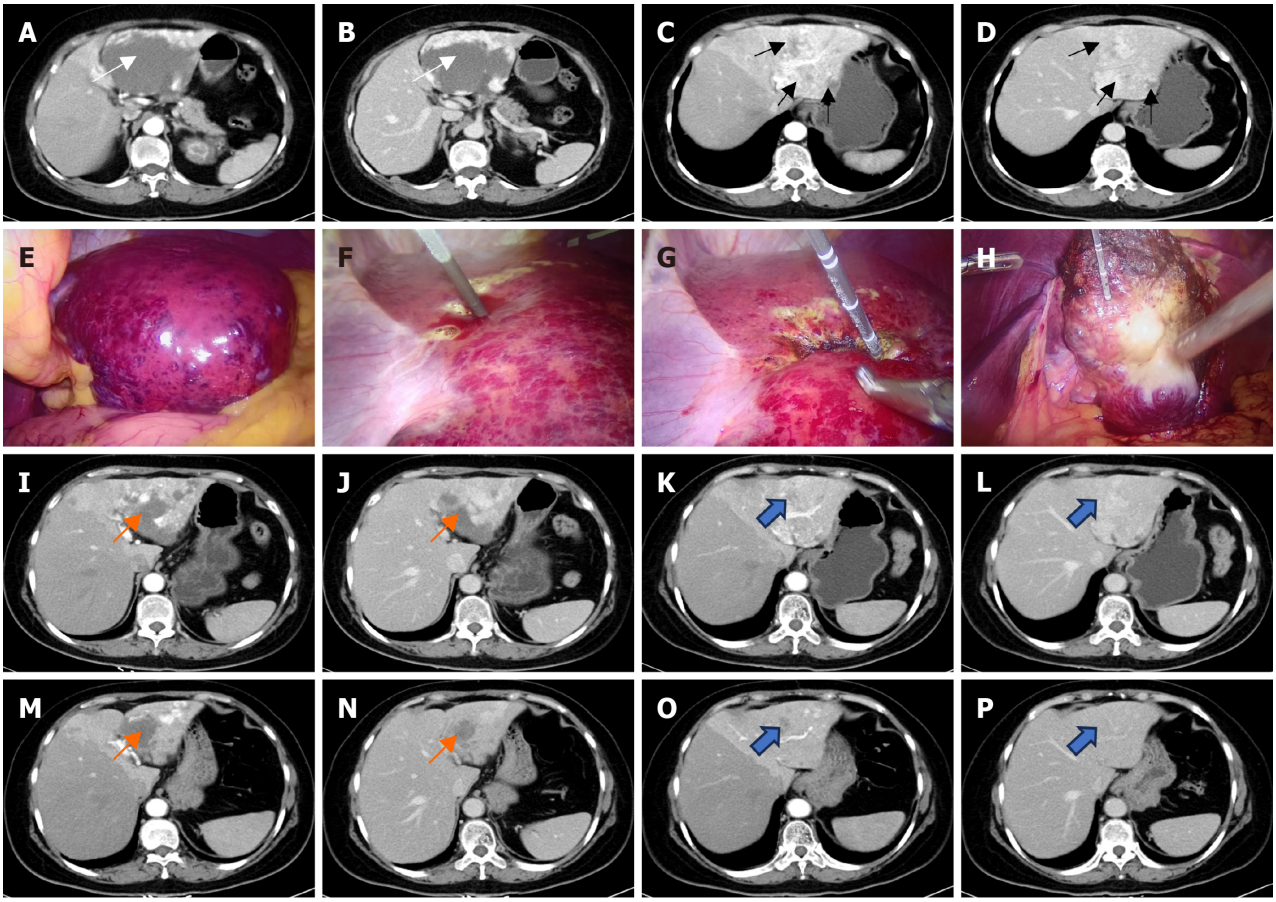

Figure 1 Initial contrast-enhanced computed tomography scan of the abdomen obtained, intraoperative findings and follow-up contrast-enhanced computed tomography scan of the abdomen obtained of case 1. A-D: Initial contrast-enhanced computed tomography (CT) scan of the abdomen obtained. A hemangioma (9.9 cm, white arrow) is evident in the left lateral segment of the liver, with multiple disseminated small enhanced nodular lesions (black arrows) adjacent to the hemangioma (A: Arterial phase; B: Arterial phase; C: Venous phase; D: Venous phase); E: Intraoperative findings of complete giant cavernous hemangioma (GCH); F: Microwave ablation of GCH, with the first application being launched from the exterior margin of the tumor; G: The second puncture point should be selected at the edge of the ablated zone rather than at the hemangioma to avoid bleeding at the puncture site. At the same time, numerous variably-sized red nodules were present near the GCH; H: After ablation, the ablated zone atrophied and collapsed; I-L: Follow-up contrast-enhanced CT scan of the abdomen obtained. Three months after ablation, contrast-enhanced CT revealed that the hemangioma was completely ablated, and the ablated zone (orange arrow) volume decreased. The reduction in the size of remained diffuse hepatic hemangiomatosis (blue arrow) was noted (I: Arterial phase; J: Arterial phase; K: Venous phase; L: Venous phase); M-P: Twenty months after ablation, contrast-enhanced CT showed that the ablated zone (orange arrow) had decreased further, with obvious shrinkage of the subtle residual diffuse hepatic hemangiomatosis (blue arrow) (M: Arterial phase; N: Arterial phase; O: Venous phase; P: Venous phase).

DISCUSSION

Hepatic hemangiomas are the most common benign liver tumors incidentally detected in most patients. DHH is a rare disease characterized by ill-defined tissue with a similar histological presentation to typical cavernous hemangiomas, replacing the hepatic parenchyma[5,8,9]. Histological features of DHH include irregularly dilated non-anastomotic vascular spaces lined with flat endothelial cells, infiltration of the native hepatic parenchyma without any encapsulation, and the latter two features distinguishing it from a cavernous hemangioma. However, hemangiomatosis is not rare in the liver parenchyma adjacent to a GCH[5]. Jhaveri *et al*[5] evaluated 41 patients who had undergone CT or magnetic resonance imaging (MRI) with reported GCH. They found 42 GCHs identified in 41 patients, and hemangiomatosis was present in 18 of 41 patients (44%). The extent of liver tissue involved by hemangiomatosis was variable but was confined to the same lobe as the GCH in the majority of patients (13/18).

As previously explained, enucleation is preferred when feasible for symptomatic GCH[10]. However, for GCH coexistent with DHH around the hemangioma, surgical candidates must be carefully selected to avoid surgical complications related to excessive blood loss from oozing due to the deroofing of the areas of hemangiomatosis after the enucleation of a GCH[5]. These cases can be better managed by extensive lobectomy, as the GCH may have small hemangiomatous lesions around the hemangioma, and large surgical margins are needed. When the tumor exceeds a certain volume in patients with limited hepatic reserve, liver resection is precluded. Liver transplantation should be considered for nonresectable benign hepatic neoplasms in patients with imminent life-threatening complications, an underlying liver disease, or the presence of severe symptoms[11]. In current published literature, there have been a total of 6 reported cases of GCH with DHH undergoing surgical intervention. In these 6 cases, 5 GCHs with DHH around the hemangioma underwent enucleation (one case)[3], extensive lobectomy (three cases)[12-14], and liver transplantation

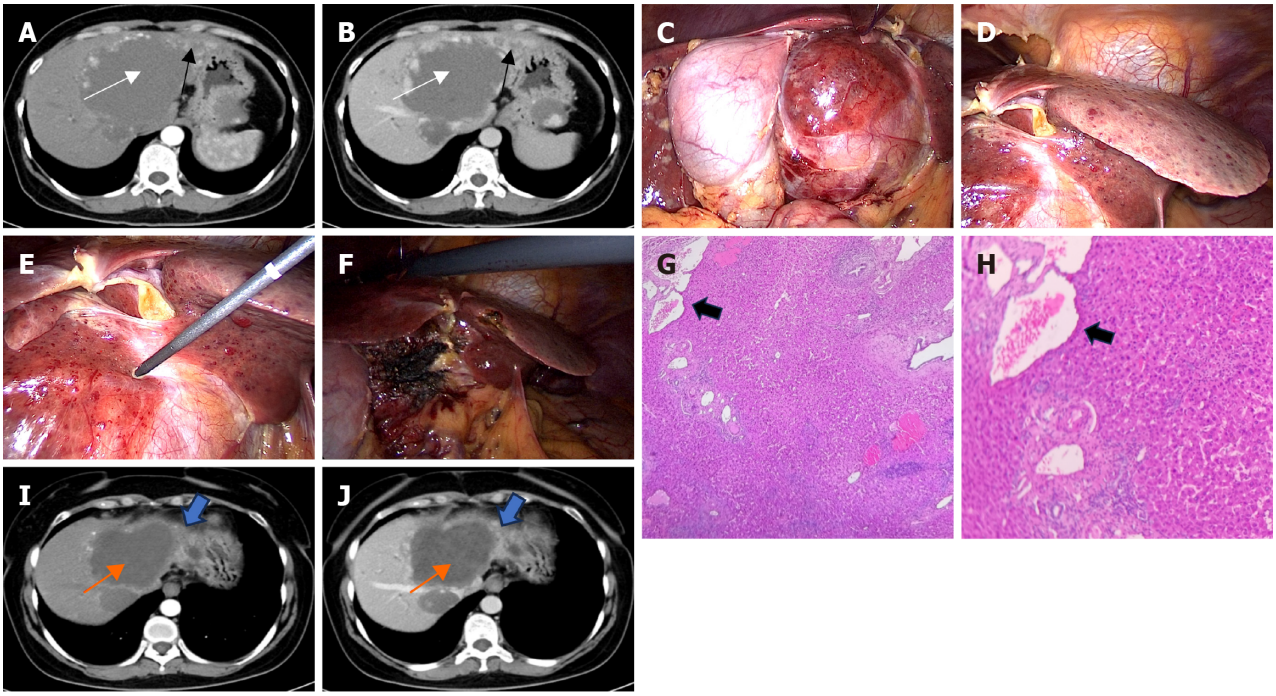

Figure 2 Initial contrast-enhanced computed tomography scan of the abdomen obtained, intraoperative findings, histological findings of resected liver tissue and follow-up contrast-enhanced computed tomography scan of the abdomen obtained of case 2. A and B: Initial contrast-enhanced computed tomography (CT) scan of the abdomen obtained. A hemangioma (10.7 cm, white arrow) is evident in the liver, with multiple disseminated small enhanced nodular lesions (black arrow) adjacent to giant cavernous hemangioma (GCH) (A: Arterial phase; B: Venous phase); C: Intraoperative findings of complete GCH; D: Multiple small hemorrhagic blood-filled honeycomb areas from 2-3 mm up to 3 cm in diameter were scattered adjacent to the GCH throughout the entire left lobe; E: The first application was launched from the exterior margin of the GCH; F: After ablation, the ablated zone atrophied and collapsed. Diffuse hepatic hemangiomatosis was left in situ without ablation; G and H: Histological findings of resected liver tissue revealed that the large majority of the portal tracts and the central veins showed expansion due to the formation of micro-angiomas along with dilatation of the native vessels. And micro-angiomatous lesions characterized by irregular-shaped dilated vascular channels arranged along with sinusoidal dilatation with some accompanied by tumor-like proliferation and red blood cell siltation seen in the lumen, and the stroma was hyperplastic fibrous tissue. The lesion was lined with flat endothelial cells without cellular atypia (black arrowhead). This lesion was diagnosed as hemangiomatosis (hematoxylin and eosin staining, G: 5 ×; H: 10 ×); I and J: Follow-up contrast-enhanced CT scan of the abdomen obtained. Three months after ablation, contrast-enhanced CT revealed that the hemangioma was completely ablated, and the ablated zone (orange arrow) volume decreased; The reduction in the size of remained diffuse hepatic hemangiomatosis (blue arrow) was noted (I: Arterial phase, J: Venous phase).

(one case)[11] respectively. Only one giant hepatic hemangioma was accompanied by DHH distributed throughout the liver, which received liver transplantation (Table 1)[15]. In fact, liver transplantation should be considered for hepatic hemangioma with DHH distributed throughout the entire liver. For hepatic hemangioma with DHH around the hemangioma, the target of treatment is the hemangioma. However, hemangiomatosis adjacent to the hemangioma does not require intervention.

In recent years, thermal ablation techniques, including RF ablation and MW ablation, have gained prominence in the treatment of hepatic hemangiomas due to advantages, such as minimal invasiveness, high efficacy, safety, rapid recovery, and broad applicability[1]. RF and MW ablation utilize heat generated by high-frequency alternating current or electromagnetic waves to disrupt endothelial cell-lined vascular structures, promoting thrombosis, inducing necrotic coagulation, destroying erythrocytes, and causing vascular smooth muscle cell loss and fibrosis in the ablated zone[16]. MW ablation offers certain advantages over RF ablation, including the creation of a larger necrotic area of necrosis, shorter treatment times, and reduced sensitivity to the conductivity of surrounding tissues caused by the heat-sink effect[17]. Success in this study relied on extensive experience, adherence to detailed treatment protocols, precise imaging guidance, and accurate antenna placement[18]. The puncture direction of the MW ablation antenna should be as parallel as possible to significant intrahepatic tracts. Additionally, when the MW antenna is positioned more than 2.0 cm away from hepatic vessel, vascular cooling effects help safeguard peritumoral vessels from damage[1]. Direct puncturing of normal liver parenchyma by the MW antenna should be avoided. After each ablation, the antenna is repositioned to target areas using the overlapping ablation method, particularly for large tumors[18]. Real-time visualization of the antenna trajectory is critical to prevent damage to bile ducts and hepatic vessels. Ablation is halted when microbubbles form near the antenna tip in proximity to major vessels or bile ducts, as monitored by intraoperative US guidance. Routine postprocedural imaging, alongside close monitoring of blood counts, coagulation profiles, hepatorenal function tests, and urine analysis, is strongly recommended[19]. Following ablation, the edge of the ablation zone shifted farther from peritumoral vessels due to tumor volume reduction, contributing to the alleviation of clinical symptoms[2]. In addition, all operators were required to observe MW ablation performed in a minimum of 10 patients at a center with more experience prior to commencing MW ablation at their own institution, which may provide the critical threshold knowledge to master the MW ablation technique. And many of the smaller centers were required to perform MW ablation only in straightforward

Table 1 Retrievable reports on surgical treatment of giant cavernous hemangioma coexistent with diffuse hepatic hemangiomatosis

Year	Clinical features	The largest GCH location	The largest GCH size, cm	DHH distribution	Treatment	Operation time, minutes	Intraoperation blood loss, mL	Postoperative length of stay, days	Follow up	Prognosis
2000	Post-prandial epigastric discomfort	Right lobe	17 × 14 × 9	Locally	Right hepatectomy	NA	NA	14	9 months	No recurrence
2014	Epigastric pain and abdominal fullness	Right lobe	20 × 14 × 8.5	Locally	Extensive right hepatectomy	190	845	9	NA	NA
2018	Abdominal pain, hepato-megaly	Central portion of the liver	16	Locally	Liver transplantation	575	1100	11	1.5 year	No recurrence
2020	NA	Segment IVb	7.8	Locally	Left hepatectomy	NA	NA	12	1 year	No recurrence
2021	Abdominal pain and distension	Segment IV	32 × 23 × 20	Throughout the liver	Liver transplantation	660	3000	16	6 months	No recurrence
2022	Right upper quadrant fullness	Left lobe	11 × 8 × 11.3	Locally	Enucleation	NA	NA	5	6 months	No recurrence

No Complication was observed in these cases. GCH: Giant cavernous hemangioma; DHH: Diffuse hepatic hemangiomatosis; NA: Not available.

cases, and refer more difficult cases to the larger centers.

Herein, we report two patients with GCH coexistent with DHH successfully treated by laparoscopic MW ablation. The two patients presented without severe complications during hospitalization and were in generally good condition, thus qualifying for thermal ablation. Protruding hemangiomas and superficial hemangiomas are indications for laparoscopic thermal ablation[18]. Therefore, a laparoscopic MW ablation procedure was employed in our two cases. Due to DHH within the liver parenchyma, it was left in situ without ablation to preserve liver parenchyma. It is worth noting that, due to the perivenous hemangioma in case 2, even though the tumor is larger, we aimed to minimize the ablation time and the number of ablation sessions in order to protect the surrounding normal tissue.

To the best of current knowledge, this report is the first to investigate the safety and efficacy of thermal ablation for GCH coexisting with DHH. In the study, both patients underwent successful MW ablation. Complete ablation of the hemangiomas was achieved, and the ablated zones demonstrated significant atrophy. Notably, follow-up imaging revealed a gradual reduction and eventual diminishment of DHH. Compared to surgical therapies described in previous literature, MW ablation was associated with reduced intraoperative bleeding and a shorter postoperative hospital stay, although no statistical comparisons were performed. Both patients were discharged shortly after the procedure without any symptoms or complications. The postoperative course was uneventful, with no recurrence of liver lesions detected during follow-up. It is important to note that this report specifically addresses cases involving thermal ablation for DHH located in proximity to GCH. Further clinical studies are needed to confirm the efficacy of thermal ablation for GCH combined with diffusely distributed DHH throughout the liver.

CONCLUSION

In conclusion, we reported two patients with GCH coexistent with DHH successfully treated by laparoscopic MW ablation. Thermal ablation treatment may be an effective and less invasive treatment for GCH coexistent with DHH around the hemangioma.

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FOOTNOTES

Author contributions: Xu F collected and analyzed data and drafted the manuscript; Kong J and Dong SY were responsible for the perioperative management; Xu F and Kong J contributed equally as co-first authors; Xu L and Wang SH participated in this study; Sun WB critically revised the manuscript; Gao J performed the microwave ablation; Xu F drafted the manuscript; Sun WB and Gao J contributed equally as co-corresponding authors; and all authors agreed to take responsibility for the integrity of the data and the accuracy of data analysis, and approved the final version of the manuscript.

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CASE REPORT

Rare large sigmoid hamartomatous polyp in an elderly patient with atypical Peutz-Jeghers syndrome: A case report

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Abstract

BACKGROUND

Peutz-Jeghers (PJ) syndrome (PJS) is a rare autosomal dominant genetic disease characterized by the association of intestinal polyposis, mucosal skin pigmentation, and cancer susceptibility. PJS patients have a significantly increased risk of malignant tumors in the gastrointestinal tract and extra-gastrointestinal tract, including various epithelial malignant tumors (colorectal cancer, gastric cancer, pancreatic cancer, breast cancer, and ovarian cancer, *etc.*). PJS is commonly seen in children and adolescents with multiple small intestinal polyps, often causing intussusception.

CASE SUMMARY

A 62-year-old male presented with intermittent left lower abdominal pain after drinking or consuming cold beverages that was accompanied by occasional hematochezia. Abdominal contrast-enhanced computed tomography indicated an isolated sigmoid colon grape-like lesion. Subsequently, the patient underwent laparoscopic surgery, and the pathological diagnosis was PJ hamartomatous polyp. PJS was not considered at the initial visit, as the patient was older, and the facial pigmentation was not obvious. However, significant pigmentation was observed in the perineum during digital rectal examination. Interestingly, we observed that the patient exhibited nodular shadows in the adrenal glands computed tomography images that may be related to pigmentation. Therefore, we performed the determination of adrenal cortical hormones, but the results were not abnormal. Combined with skin and mucosal pigmentation and laboratory examinations, the

patient was diagnosed with PJS. After laparoscopic sigmoid colon resection, the patient's symptoms improved, and no discomfort symptoms were reported in the later follow-up.

CONCLUSION
The age of onset and lesion location of this case are different from those of typical or isolated PJS patients.

Key Words: Peutz-Jeghers syndrome; Sigmoid colon; Large isolated colonic polyp; Skin pigmentation; Case report

Core Tip: Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant hereditary illness defined by the connection of intestinal polyposis, mucosal skin pigmentation, and cancer risk. Due to the older age, the clinical features of mucosal hyperpigmentation were atypia in this case study. Due to the location of the polyp in the sigmoid colon, the common intussusception symptoms of PJS cases in the past did not appear, and only hematochesis and abdominal pain related symptoms were observed. PJS mainly occurs in children and adolescents, often with multiple small intestinal polyps. Such an advanced age with a rare polyp location has not been reported.

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INTRODUCTION

Peutz-Jeghers (PJ) syndrome (PJS) is a rare autosomal dominant genetic disorder that is primarily manifested by three characteristics, including pigmentation in the mucous membranes of the lips, fingers, toes and perineum, multiple polyps in the gastrointestinal tract, and a familial hereditary tendency. The incidence rate is 1/50000 to 1/200000[1]. The diagnostic criteria for PJS are as follows: (1) Three or more PJ polyps confirmed by histology; (2) Individuals with a family history of PJS developing any number of PJ polyps; (3) Individuals with a family history of PJS presenting with mucocutaneous pigmentation; and (4) Any number of PJ polyps accompanied by mucocutaneous pigmentation (diagnosis of this disease can be made if any of the above criteria are met). The hamartomatous polyps of PJS most commonly occur in the small intestine (in order of prevalence: Jejunum, ileum, and duodenum) followed by the stomach and are relatively rare in the large intestine[2]. The size of PJS-related gastrointestinal polyps varies, ranging from a few millimeters to several centimeters. The polyps can be sessile or pedunculated and often occur in adolescents and during early adulthood, but they are relatively rare in elderly patients[3,4]. Xu *et al*[5] analyzed 566 patients with PJS, where male patients accounted for 55.3%, female patients accounted for 44.7%, the median age of skin and mucosal pigmentation was 2 years, and the median time interval between the age of skin pigmentation and the onset of gastrointestinal symptoms was 10 years. Matsubara *et al*[6] investigated 701 Japanese patients with PJS and juvenile polyposis syndrome (JPS) and determined that males accounted for 53.5% and 59.6% of the PJS and JPS groups, respectively. The mean age at diagnosis of PJS is 23 years in men and 26 years in women, the incidence of PJS is comparable in men and women, and there is no ethnic tendency for PJS[7].

The typical clinical manifestations of PJS are gastrointestinal symptoms such as abdominal pain, diarrhea, bloody stool, constipation, and others. Gastric and intestinal polyps can also cause anemia, intestinal obstruction, and intestinal volvulus, among other complications[5]. Approximately half of the patients experience bleeding, obstruction, and abdominal pain around the age of 20[8]. Generally, the gastrointestinal symptoms of PJS are primarily related to small intestinal polyps, while the impact of colon and rectal polyps on the gastrointestinal tract is minimal. This results in patients with PJS often experiencing lesions in the colon and rectum that are difficult to detect, leading to a later age of diagnosis.

Previous case reports of PJS predominantly focused on children and adolescents, and cases of PJS in older patients were rarely reported. Additionally, with the increase in age, melanin pigmentation on the face and palms of older patients with PJS gradually fades, particularly when PJS polyps are located in atypical sites or are solitary polyps, and the pigmentation becomes even less obvious[9]. As the faces of the elderly are often accompanied by seborrheic keratosis, clinical skin physical examinations are prone to being overlooked. At such times, it is even more necessary for clinical practitioners to pay close attention to the pigmentation in concealed areas such as the oral mucosa and perineum of patients.

This report is of a 62-year-old male who presented with left lower abdominal pain and hematochezia following alcohol or cold beverage consumption that was attributed to a giant hamartomatous polyp in the sigmoid colon. The patient underwent laparoscopic resection of a segment of the sigmoid colon that was pathologically diagnosed as PJ-like polyp. Physical examination revealed melanin deposition in the lower lip, oral buccal mucosa, fingers, and perineal area, leading to a diagnosis of PJS. The patient experienced satisfactory recovery and improvement postoperatively. Notably, this case

exhibited an older age at onset, unique disease localization, and rare occurrence of an isolated giant hamartoma polyp.

CASE PRESENTATION

Chief complaints

A 62-year-old man presented at the Anus and Intestine Surgery Department of our hospital with a one-week history of intermittent dull pain in the left lower abdomen accompanied by bloody stools.

History of present illness

The patient began experiencing intermittent dull pain in the left lower abdomen with bloody stools one week earlier after consuming alcohol and cold drinks. There were no symptoms such as fever, defecation rhythm, tenesmus, anal heaviness, emaciation, fatigue, nausea, and vomiting. Although the patient had previously noticed pain in the left lower abdomen after consuming alcohol or cold drinks, this time it was noticeably worse. The pain could resolve spontaneously in previous episodes, but this time it lasted for a week and was associated with bloody stools.

History of past illness

The patient exhibited a history of hypertension for 20 years. The patient took irbesartan and hydrochlorothiazide regularly, and his blood pressure was well controlled. There was no history of diabetes mellitus or coronary heart disease.

Personal and family history

The patient exhibited a 40-year history of smoking and drinking alcohol. There was no history of allergy or family history. No one in the family experienced similar symptoms and diseases.

Physical examination

The patient's temperature was 36.5 °C, pulse was 58 beats per minute, respiration was 17 breaths per minute, and blood pressure was 153/104 mmHg. Upon examination, the patient's vital signs remained stable. Dark brown spots were visible on the lower lip and back of the hand; however, these pigmentation spots appeared lighter compared to those typically observed in previous patients. An oral mucosa examination revealed a melanotic spot on the right buccal mucosa. Prominent pigmentation of the perineal skin was noted (Figure 1). Abdominal examination did not reveal any significant abnormal signs. Digital rectal examination was performed without detecting any masses or bleeding.

Laboratory examinations

All of the patient's laboratory examinations yielded normal results.

Imaging examinations

The abdominal contrast-enhanced computed tomography examination of the patient revealed bilateral adrenal gland thickening with an uneven pattern, accompanied by a nodular shadow. The left nodule was relatively large, measuring approximately 0.7 cm in size, and it exhibited significant enhancement on the contrast-enhanced scan (Figure 2). Additionally, there was an irregular soft tissue mass in the sigmoid colon measuring approximately 10.71 cm × 7.187 cm with a computed tomography (CT) value of approximately 46 HU (Figure 3). Colonoscopy demonstrated multiple grape-like masses located in the colon at a distance of 30-35 cm from the anal verge. The mucosa of the ascending colon, transverse colon, descending colon, sigmoid colon, and rectum appeared smooth with clear vascular texture, and no ulcers or vegetations were observed. Enteroscopy was not performed in this case. An endoscopic biopsy was conducted on the lesion tissue present in the sigmoid colon that indicated hamartomatous polyps and mucosal prodromal polyps (Figure 4). Fecal occult blood testing yielded positive results, while preoperative blood routine analysis indicated normal values. Plasma free cortisol levels and rhythm tests did not exhibit any abnormal changes.

FINAL DIAGNOSIS

Based on postoperative pathological examination, colonoscopic biopsy, and skin pigmentation, the patient was finally diagnosed with PJS.

TREATMENT

Laparoscopic partial resection of the sigmoid colon was performed. The resected bowel measured approximately 15 cm in length. The lesion was 3 cm from one stump and 6 cm from the other. The polyp size was approximately 6 cm × 5 cm × 5 cm (Figure 5).

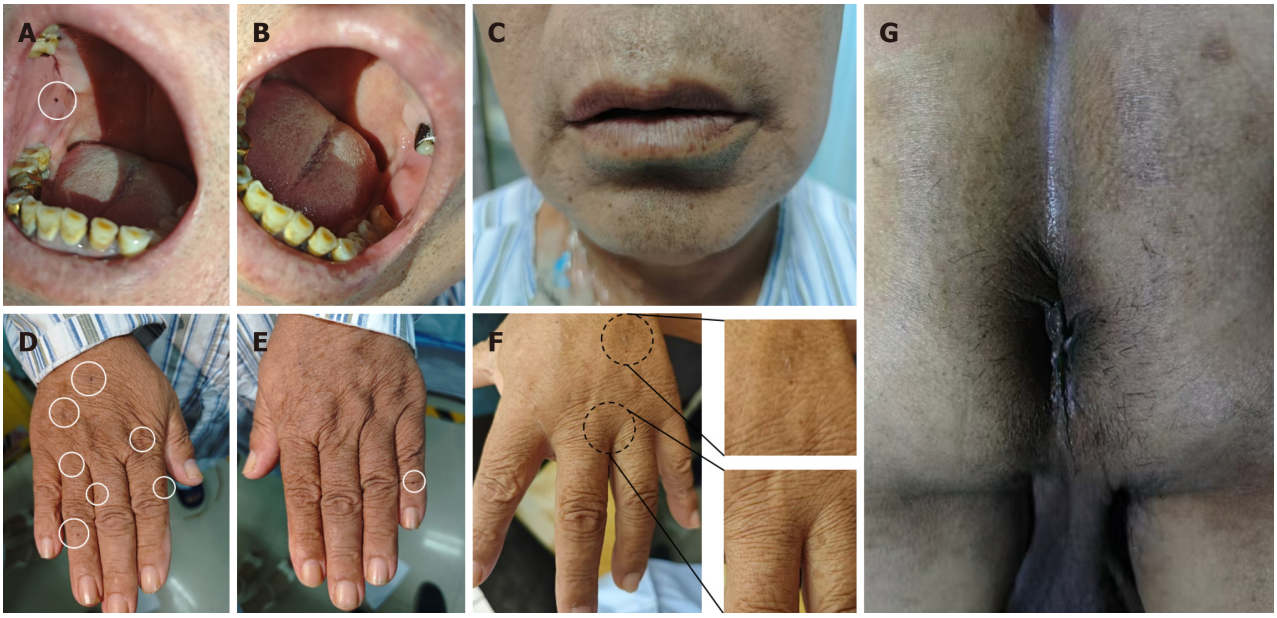

Figure 1 Melanin pigmentation of skin and mucosa of this patient. A: The patient had a spot of melanin pigmentation in the buccal mucosa on the right side; B: The left buccal mucosa of the patient was normal without pigmentation; C: The patient's lower lip was marked with melanin pigmentation, but the color was light; D-F: Pigmentation of the patient's hands; G: Pigmentation of the patient's perineum. White circles outline areas of pigmentation.

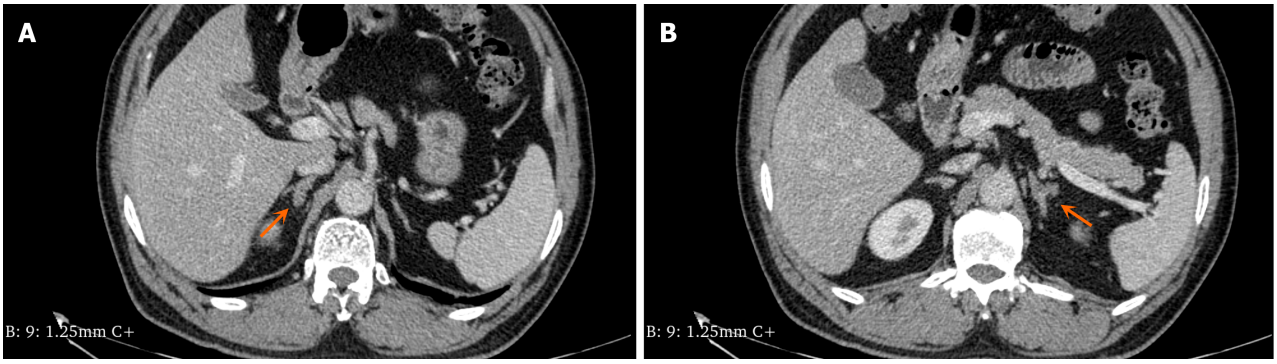

Figure 2 Contrast-enhanced computed tomography of bilateral adrenal glands. A: Imaging of the right adrenal gland; B: Imaging of the left adrenal gland.

OUTCOME AND FOLLOW-UP

Hematoxylin-eosin staining of the lesion samples revealed dendritic extension of smooth muscle from the mucosal muscle layer to the epithelial cells, with normal mucosal epithelium covering its surface. Local growth of the lesion exhibited active progression without abnormal hyperplasia, and there were no notable changes observed in both ends of adjacent bowel or surrounding lymph nodes (Figure 5). The pathological diagnosis confirmed PJ polyp, and this combined with clinical symptoms such as skin pigmentation led to a final diagnosis of PJS. The patient experienced a smooth recovery after surgery, complete disappearance of symptoms, and no significant discomfort during follow-up.

DISCUSSION

The definition of PJS is an autosomal dominant disorder, also known as familial hamartomatous polyposis syndrome [10]. It is characterized by the presence of hamartomatous polyps in the gastrointestinal tract, particularly in the small intestine, along with pigmented mucocutaneous lesions[11,12]. Hamartomatous polyps are characterized by bundles of smooth muscle that extend dendritically into the lamina propria and are overlaid with nearly normal epithelium. The surface epithelium of hamartomatous polyps was identical to the adjacent normal mucosal epithelium. Mucocutaneous pigmentation typically occurs in infancy and resolves later in life, typically in late adolescence[13]. These lesions are due to the presence of pigment-rich macrophages in the dermis, dark brown or blue-brown color, and sizes ranging from 1 mm to 5 mm.

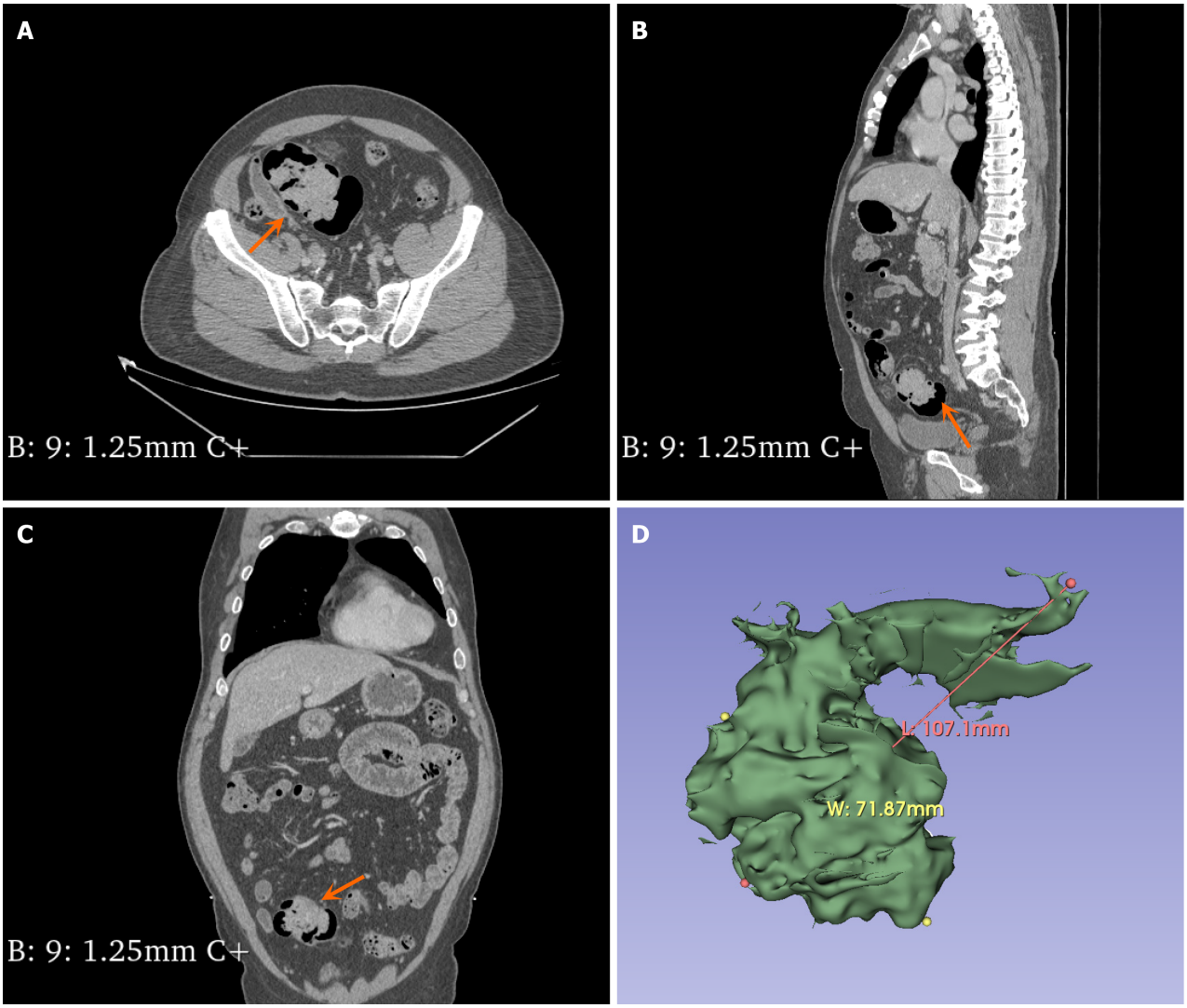

Figure 3 Contrast-enhanced computed tomography of the abdomen. A: The sigmoid colon mass was observed in the horizontal plane; B: The sigmoid colon mass was observed in the sagittal planes; C: The sigmoid colon mass was observed in the coronal planes; D: 3D reconstruction model of sigmoid colon mass. The orange arrow points to the sigmoid mass.

PJS is an autosomal dominant inherited disease caused by the mutation of the tumor suppressor gene STK11/LKB1, and this disease is characterized by multiple polyps in the gastrointestinal tract, skin and mucosal pigmentation, and susceptibility to malignant tumors[14,15]. Li *et al*[16] reported that compared to normal gastrointestinal mucosa, the promoter methylation level of the LKB1 gene in PJS polyps was typically increased, but the methylation pattern of different PJS polyps was also different. The study observed that hypomethylation in PJS patients was closely related to gastrointestinal malignant tumors. The change in methylation level may be the result of the influence of diet, the environment, and other factors. Due to family economic difficulties, chromosome and family tree gene analyses were not performed. The patient indicated that no other family members experienced symptoms, and we recommended that his children undergo regular gastroenteroscopy.

In general, PSJ often occurs in young children, and the increase and enlargement of gastrointestinal polyps can cause various complications such as intussusception, intestinal obstruction, gastrointestinal bleeding, cancerization, and malnutrition. In addition to the typical skin mucosa and multiple polyps of the gastrointestinal tract, some patients can be characterized as only melanin with no gastrointestinal polyps or as only gastrointestinal polyps with no melanin, and this is called incomplete PJS and is an incomplete explicit genetic performance that may be related to environmental factors [17,18]. In this case, the affected area is the sigmoid colon, and it exists as a solitary giant hamartoma that is very rare in PJS. Due to anatomical reasons, intussusception in adults is less common than it is in children, and intussusception in the rectum and colon is less common than that in the proximal intestine[19]. The patient's age and the unusual position of the PJ polyps led to late onset of symptoms, with the predominant symptoms being hematochezia and intestinal spastic abdominal pain caused by alcohol or cold drinks. Although the pigmentation of the lower lip, palm, and fingers had faded with age, the pigmentation of the oral mucosa and perineal region remained visible. Hypopigmentation in elderly patients poses a considerable challenge for our diagnosis of PJS. Hence, we need to collect and follow up on a large-scale PJS patients in the following steps and systematically categorize their characteristics based on different age groups. Additionally, seborrheic keratosis is often present on the faces of elderly individuals. To discriminate this from the

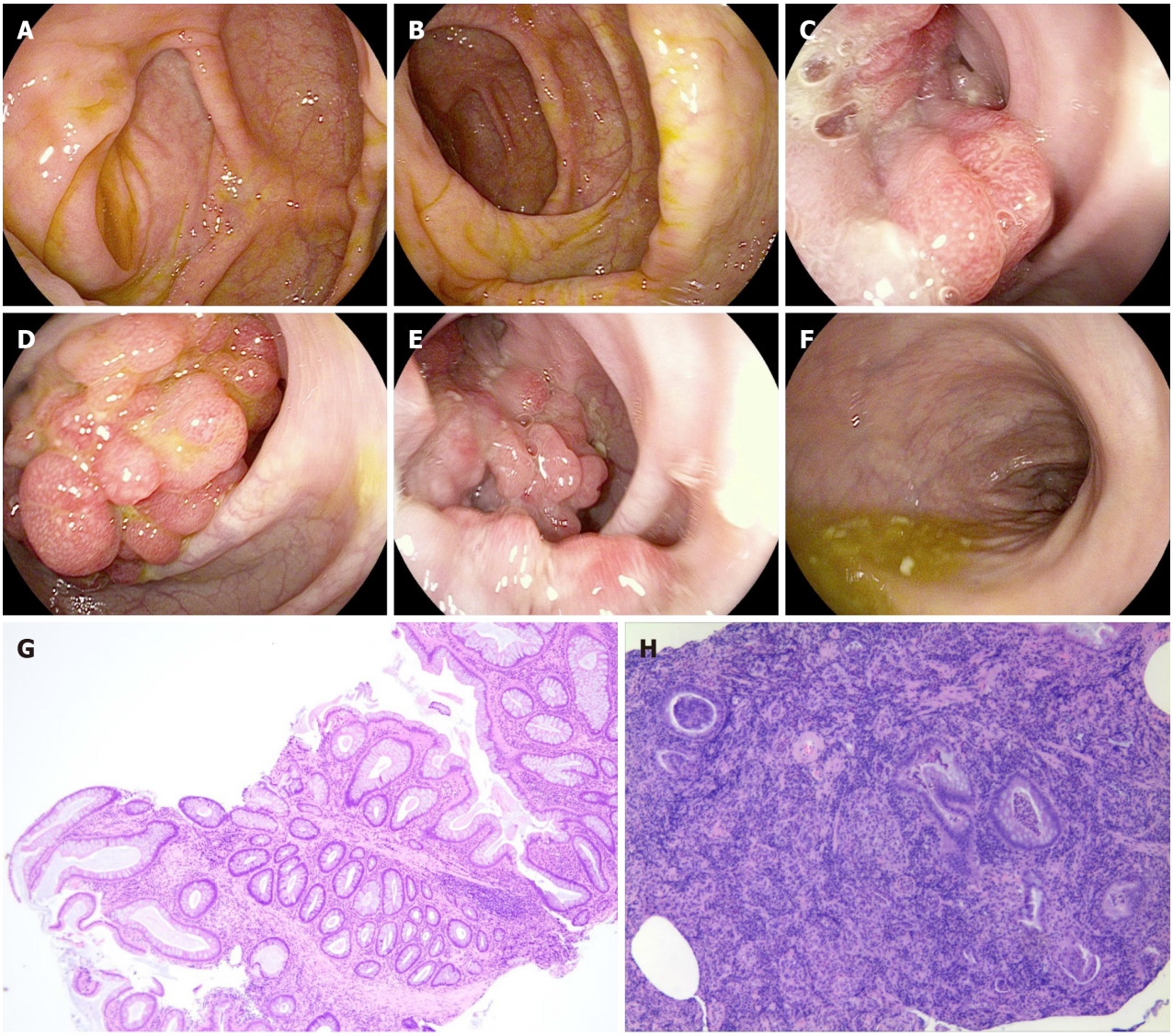

Figure 4 Colonoscopy and endoscopic forceps were used to obtain tissue pathological biopsy. A: The appendiceal fossa mucosa was smooth without dysplasia or polyps; B: The ileocecal mucosa was smooth and no ulcer or neoplasm was observed; C-E: A grape-like mass was seen in the sigmoid colon 30 cm to 35 cm from the anal verge; F: No abnormal lesions were found in the rectum; G: Pathological changes of hamartomatous polyps; H: Pathological examination showed mucosal prolapsed changes and ulcer formation in some areas.

depigmented macules of PJS, clinicians need to carefully observe the skin conditions of the limbs, oral mucosa, and perineum to avoid misdiagnosis of PJS.

Additionally, it is interesting that the abdominal CT of this patient revealed nodules in the adrenal gland. Combined with the pigmentation of the patient, we considered whether the patient's pigmentation was caused by adrenal nodules and adrenal insufficiency[20]. Subsequently, we performed adrenocortical hormone measurements that indicated normal adrenocortical hormone secretion, and this also ultimately supported the diagnosis of PSJ. This case prompts our thinking and clinical differential diagnosis of skin hyperpigmentation related diseases. Skin pigmentation is a prominent feature of primary adrenal insufficiency such as Addison's disease[21]. This pigmentation caused by Addison's disease is observed primarily on sun-exposed areas, scars, armpits, nipples, palm folds, pressure points, and mucous membranes (including the cheeks, vagina, vulva, and anus)[22]. The cause of this hyperpigmentation is generally believed to be due to increased stimulation of the melanocyte-stimulating hormone receptor (MC1R) by adrenocorticotropic hormone (ACTH) itself[23]. Pigmentation in PJS occurs primarily in the lower lip, mouth, limbs, and perineum, it appears at birth and in early childhood, and it increases during adolescence. They may become inconspicuous in adulthood but are typically still present on the buccal mucosa without abnormal hormonal changes.

Patients with PJS exhibit a higher risk of malignancies at different sites, including gastrointestinal and extra-gastrointestinal cancers. However, the carcinogenic mechanism of this disease is not fully understood. Currently, in addition to surgery and routine endoscopic polypectomy, there is no precision medicine for treatment and prevention, and only surveillance can be performed. Wang *et al*[24] discussed the hamartoma-adenoma-carcinogenesis pathway in their research. Although the small intestine is the most commonly involved site of the characteristic hamartomatous polyps of PJS, the incidence of malignancy in the small intestine has been observed to be much lower than that in the colorectum. In this patient, no malignant transformation was identified, but regular screening colonoscopy has been recommended[24].

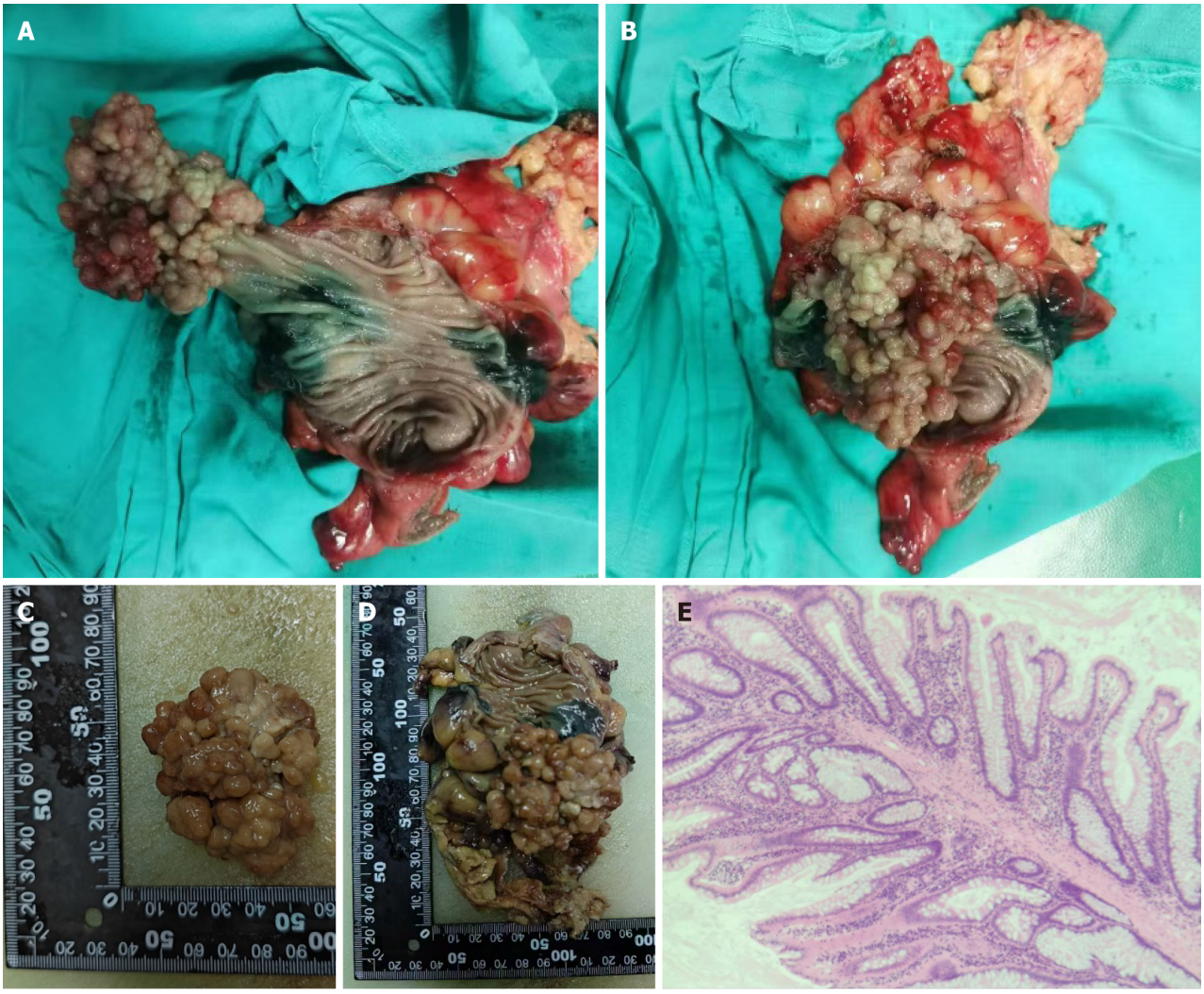

Figure 5 Postoperative tissue sample and pathological results. A-D: The resected grape-like mass of sigmoid colon was showed and the polyp size was approximately 6 cm × 5 cm × 5 cm; E: Hematoxylin-eosin staining of the lesions. There were dendritic-like structures formed by the proliferation of muscle fibers in the muscularis mucosa, which were overlaid with intrinsic mucosa tissue and piled up into villous structures.

CONCLUSION

In conclusion, the age, location, predisposing factors, and differential diagnosis of this case can provide important reference value for clinical practice. The report of this case will enrich our understanding of the view that PJS patients of different ages exhibit different signs. Concurrently, for elderly patients with abdominal pain and hematochesia, we should pay more attention to some local signs that may provide us with unexpected ideas for the diagnosis of related diseases.

FOOTNOTES

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LETTER TO THE EDITOR

Role of two-dimensional shear wave elastography in predicting post-hepatectomy liver failure: A step forwards in hepatic surgery

Hua-Zhen Deng, Yu-Feng Liu, Han-Wen Zhang

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Abstract

This study explores the significance of using two-dimensional shear wave elastography (2D-SWE) to assess liver stiffness (LS) and spleen area (SPA) for predicting post-hepatectomy liver failure (PHLF). By providing a non-invasive method to measure LS, which correlates with the degree of liver fibrosis, and SPA, an indicator of portal hypertension, 2D-SWE offers a comprehensive evaluation of a patient's hepatic status. These advancements are particularly crucial in hepatic surgery, where accurate preoperative assessments are essential for optimizing surgical outcomes and minimizing complications. This letter highlights the practical implications of integrating 2D-SWE into clinical practice, emphasizing its potential to improve patient safety and surgical precision by enhancing the ability to predict PHLF and tailor surgical approaches accordingly.

Key Words: Two-dimensional shear wave elastography; Liver stiffness; Spleen area; Post-hepatectomy liver failure; Non-invasive techniques; Hepatic surgery

Core Tip: Two-dimensional shear wave elastography offers a non-invasive method to predict post-hepatectomy liver failure, enhancing preoperative assessment and patient outcomes in hepatic surgery.

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TO THE EDITOR

Post-hepatectomy liver failure (PHLF) remains a significant concern in hepatic surgery, impacting both patient outcomes and health care resources[1]. Recent advancements in noninvasive imaging techniques have provided new avenues for improving preoperative assessments. Among these, two-dimensional shear wave elastography (2D-SWE) has emerged as a promising tool for evaluating liver stiffness (LS) and the spleen area (SPA), both of which are critical parameters for predicting PHLF[2,3].

Significance of 2D-SWE in hepatic surgery

The authors have significantly advanced the field of hepatic surgery by demonstrating the utility of 2D-SWE in accurately assessing LS and SPA. The use of 2D-SWE in hepatic surgery has shown considerable promise due to its ability to provide accurate measurements of LS[4]. LS is directly associated with the degree of liver fibrosis, which is a critical factor in determining the liver's functional reserve. By offering a non-invasive method to assess LS, 2D-SWE eliminates the need for more invasive procedures like liver biopsy, reducing patient risk and discomfort. This technique not only simplifies the preoperative evaluation process but also enhances the accuracy of liver condition assessments, leading to more informed surgical planning.

In addition to evaluating LS, 2D-SWE also measures SPA, which serves as an indirect marker of portal hypertension. Portal hypertension is a significant predictor of PHLF, as it indicates increased pressure in the portal venous system, often associated with advanced liver disease and poor postoperative outcomes[5]. By integrating SPA measurements, 2D-SWE provides a comprehensive evaluation of the patient's hepatic and splenic status, offering valuable insights into their risk profile for PHLF. This dual assessment capability makes 2D-SWE an invaluable tool in the preoperative setting, enhancing the ability to predict and mitigate potential complications[6].

Implications for clinical practice

The authors' work holds significant implications for clinical practice, offering a noninvasive method to enhance the precision of preoperative risk stratification for PHLF[4]. Integrating 2D-SWE into routine preoperative evaluation protocols could revolutionize clinical practice by improving the precision of risk stratification for PHLF[7]. Surgeons and hepatologists can utilize this technology to deepen their understanding of the patient's liver condition, enabling more tailored and strategic surgical approaches. This personalized care model is crucial for optimizing surgical techniques and postoperative management plans on the basis of the individual risk profile determined by 2D-SWE, leading to improved patient outcomes.

Furthermore, the noninvasive nature of 2D-SWE offers practical advantages in clinical settings. By reducing the need for invasive procedures and associated complications, 2D-SWE not only improves patient safety but also enhances the overall efficiency of preoperative assessments[8]. Accurate prediction of PHLF through noninvasive screening can enhance resource allocation and streamline patient care pathways, ultimately improving the overall quality of hepatic surgery services. As more clinicians integrate this technology, a significant shift towards more proactive and preventive surgical care strategies can be expected[9].

Future directions

While the current findings are promising, further research is needed to validate these results across larger and more diverse patient populations. Additionally, combining 2D-SWE with other diagnostic modalities may lead to more robust predictive models[10]. The continuous evolution of noninvasive technologies will undoubtedly play a pivotal role in shaping the future of hepatic surgery.

Conclusion

The adoption of 2D-SWE for evaluating LS and the SPA represents a significant advancement in the preoperative assessment of patients undergoing hepatic surgery. Its ability to predict PHLF noninvasively not only improves clinical outcomes but also enhances patient safety. As we continue to refine these techniques, the future of hepatic surgery looks promising, offering us more effective tools to address the challenges of liver disease.

FOOTNOTES

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LETTER TO THE EDITOR

Enhancing endoscopic retrograde cholangiopancreatography safety: Predictive insights into gastric retention

Asad Gul Rao, Abdulqadir J Nashwan

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is a vital tool for diagnosing and treating biliary and pancreatic disorders, but its safety and efficacy are marred by preoperative gastric retention. Jia *et al* retrospectively analyzed 190 patients who underwent ERCP and found that gastrointestinal obstruction, jaundice, opioid use, female sex, and primary diseases were independent predictors and risk factors of preoperative gastric retention. Based on these findings and comprehensive analysis, a proposed predictive model offers clinicians valuable tools to tailor preoperative strategies, improving the procedural safety and efficacy of ERCP. Despite having several limitations, like single-center design and limited generalizability, the study marks a significant advancement in optimizing ERCP outcomes through predictive analytics. Further research with larger populations and prospective designs is warranted to establish these findings.

Key Words: Endoscopic retrograde cholangiopancreatography; Gastric retention; Gastroparesis; Preoperative assessment

Core Tip: This article highlighted the groundbreaking study by Jia *et al*, which revealed that sex, jaundice, primary disease, opioid use, and gastrointestinal obstruction can exclusively contribute to the occurrence of gastric retention for patients undergoing endoscopic retrograde cholangiopancreatography. Despite several limitations, the study reflects profound clinical implications while suggesting additional research and innovative treatment approaches.

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TO THE EDITOR

Endoscopic retrograde cholangiopancreatography (ERCP) is a crucial diagnostic and therapeutic modality widely used to assess and manage biliary and pancreatic disorders. Since its introduction, ERCP has transformed the approach to ascending cholangitis, pancreatitis, choledocholithiasis, and biliary strictures. The use of ERCP in outpatient departments has also expanded dramatically due to its growing popularity and great potential in the surgical field[1]. A study found that in 2016 alone, over 150000 people underwent ERCP for various diseases[2]. By integrating endoscopy and fluoroscopy, ERCP allows for direct visualization and intervention in the biliary and pancreatic ducts, providing the combined benefit of diagnosis and prompt treatment, like stone removal, stent implantation, and tissue biopsy[3].

However, the success and safety of ERCP can be compromised by several factors, one of which is preoperative gastric retention. Gastric retention refers to the abnormal accumulation of gastric contents, leading to the obstruction of the passage of the endoscope through the gastrointestinal (GI) tract, thereby complicating the procedure[4]. This can result in prolonged procedure times, a higher aspiration risk, subpar visibility, and hindered communication with the target ducts. Additionally, it may result in postoperative complications like longer recovery periods, nausea, and vomiting[5]. Thus, it is imperative to address gastric retention and evaluate its risk factors preoperatively to optimize the outcomes of ERCP and ensure patient safety. However, few studies evaluate the various risk factors associated with gastric retention. In this critical context, Jia *et al*[6] analyzed the factors influencing preoperative gastric retention in ERCP and established a predictive model.

Factors influencing gastric retention

The retrospective study by Jia *et al*[6] was conducted on 190 individuals who underwent ERCP between January 2020 and February 2024. To ensure the reliability of the result, the study population was split into two groups: A modeling group (n = 152) and a validation group (n = 38). Patients within the modeling group were subdivided into those with preoperative gastric retention (n = 52) and those without it (n = 100). Gastric retention was identified with various clinical findings, including nausea, vomiting with undigested food, dull and colicky abdominal pain, and residual contents observed in the endoscopic visualization. After identifying important predictors of preoperative gastric retention through univariate and multivariate logistic regression analyses, the researchers constructed a predictive model that was rigorously validated using statistical methodologies like calibration curves and receiver operating characteristic analysis.

Jia *et al*[6] reported that the univariate and multivariate analyses determined five independent preoperative gastric retention predictors, including female sex, primary disease, jaundice, opioid use, and GI obstruction[6]. The probability of developing gastric retention before ERCP was significantly correlated with each of these variables. Moreover, the potential usefulness of the predictive model for these factors in clinical practice was highlighted by its high degree of performance. As reported, the area under the curve for the prediction model was 0.842 in the validation set and 0.901 in the training set, reflecting remarkable accuracy. The fact that the calibrated slope of the model was close to 1 indicated good consistency between the predicted and actual risk of aspiration[6]. Interestingly, Jia *et al*[6] found that age, body mass index, hypertension, and diabetes were not significantly associated with preoperative gastric retention.

The efforts made by Jia *et al*[6] in identifying different predicting factors for gastric retention in patients undergoing ERCP are to be congratulated. Implementing univariate and multivariate logistic regression analyses ensured the determination of independent predictors of preoperative gastric retention. This rigorous approach aided in isolating the most substantial factors, providing compact and actionable insights for clinical practice. This thorough analysis strengthened the reliability of the predictive model by ensuring that all pertinent variables were considered. Additionally, the high area under the curve values for the predictive model imply that it has tremendous discriminative ability, making it a reliable tool for predicting preoperative gastric retention. Moreover, including a validation group to confirm the performance of the model increased its clinical applicability.

However, this study had several limitations and shortcomings that should be considered. Firstly, it was a single-center study, which restricts the generalizability of the findings as there are considerable regional and institutional variations in patient demographics, clinical practices, and healthcare settings. Secondly, although Jia *et al*[6] observed several significant predictors of preoperative gastric retention, it is possible that they missed additional crucial confounding factors that could have affected stomach motility and retention, such as dietary habits, medication adherence, and previous GI surgeries. Thirdly, the study did not evaluate the efficacy of specific preoperative interventions based on the identified predictors. Comprehending the impact of customized interventions, like modifications to opioid consumption or preoperative nutritional support, on outcomes may yield practical recommendations for enhancing patient care. Lastly, the study did not discuss the interesting findings that major factors like age, body mass index, and hypertension were not significantly associated with the increased risk of gastric retention.

The study by Jia *et al*[6] sheds light on critical factors influencing preoperative gastric retention in patients undergoing ERCP, offering a predictive model with significant clinical implications. Sex-specific variations in the GI anatomy, gastric motility, and hormonal factors may impact GI function differently in males and females. This may account for the finding that female patients are more likely to experience gastric retention[6,7]. Primary diseases of the pancreas and biliary tract,

GI obstructions, and jaundice were also found to be significant predictors of gastric retention by Jia *et al*[6]. This is likely due to the direct impact of these diseases on digestive and hepatic processes, which ultimately result in delayed gastric emptying[8]. Opioids also emerged as a crucial factor due to their well-known side effects on gastrointestinal motility. It is well understood that they can significantly slow digestive processes, leading to prolonged gastric emptying[9]. Jia *et al*'s model introduced an important tool for pre-procedural risk stratification[6]. Nevertheless, the model could benefit from prospective validation and further refinement, possibly leveraging machine learning algorithms to enhance accuracy. Future research should focus on integrating such tools into pre-ERCP workflows to improve real-time clinical decision-making.

The clinical implications of this study[6] are profound. Due to the close correlation between gastric retention and primary disorders of the biliary system and pancreas, it is crucial to conduct comprehensive preoperative assessments that include an in-depth evaluation of the underlying primary disease, specifically focusing on its impact on gastric motility. High-risk patients identified through the predictive model could benefit from tailored preoperative protocols, such as extended fasting periods or nasogastric decompression, to reduce gastric content volume and improve procedural conditions. Because there is a strong association between jaundice and gastric retention, clinicians should prioritize liver function optimization in jaundiced patients before ERCP. This could entail dietary assistance, biliary drainage techniques, and other focused treatments to enhance digestive function. Furthermore, the link between opioid use and increased gastric retention underscores the need for careful surveillance of opioid therapy and the possible inclusion of prokinetic drugs and integration of opioid stewardship programs, such as dose adjustments or opioid-sparing alternatives, can improve both gastric motility and procedural success. In addition, implementing the predictive model in clinical practice and its incorporation into the electronic medical record systems to automatically flag high-risk patients based on input parameters can allow for real-time clinical decision support and optimization of preoperative strategies.

CONCLUSION

The study by Jia *et al*[6] highlighted important associations in understanding and predicting preoperative gastric retention in patients undergoing ERCP. By identifying key factors like sex, primary disease, jaundice, opioid use, and GI obstructions, the study offered a comprehensive predictive model with high accuracy. These findings emphasized the significance of targeted preoperative evaluations and interventions adjusted to individual patient risk profiles. The strengths of the study, mainly the thorough statistical analysis and practical clinical implications, make it a valuable tool for improving patient outcomes for future clinical care. However, addressing the limitations through larger studies with a prospective, multicenter design will be essential for validating the generalizability of the findings. Overall, the predictive model proposed in this study holds significant promise for enhancing preoperative care, reducing perioperative complications and increasing the success of ERCP procedures.

FOOTNOTES

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LETTER TO THE EDITOR

Clinical benefits and controversies of jejunostomy feeding in patients undergoing gastrectomy for gastric cancer

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Abstract

Globally, gastric cancer ranks as the fifth most common malignancy and the third leading cause of cancer-related mortality. Gastrectomy combined with perioperative chemotherapy is currently the standard of care in locally advanced stages, but the completion rate of multimodal approach is influenced also by patient related factors. Malnutrition is a well-known risk factor associated with poor oncological outcomes. Its perioperative supplementation could lead to an improvement of the nutritional status. This article reviews and comments the retrospective study conducted by Jaquet *et al,* which evaluates the impact of enteral nutrition by jejunostomy feeding in patients undergoing gastrectomy for cancer. The authors included 172 patients, 35% of whom received jejunostomy. Patients with optimized biological nutritional parameters (body mass index, albumin, prealbumin) showed reduced major complications (> III), according to the Dindo-Clavien classification, 0 (0%) *vs* 8 (4.7%) (P = 0.05). In the era of multimodal treatment, optimization of nutritional and performance status is integral part of the therapeutic strategy.

Key Words: Gastric cancer; Feeding jejunostomy; Malnutrition

Core Tip: Malnutrition is a widely recognized risk factor linked to unfavorable oncological outcomes. Enteral nutrition has many advantages, including immune and intestinal mucosa support, avoidance of bacterial translocation, and decreased risk of venous catheter infection. With perioperative chemotherapy now established as the standard treatment for advanced gastric cancer, the discussion about the benefits of jejunostomy placement for nutritional support during diagnostic exploratory laparoscopy or major surgical procedures remains particularly pertinent.

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TO THE EDITOR

Every year, around 990000 people are diagnosed with gastric cancer worldwide, of whom approximately 738000 died. Gastric cancer is the fourth most common incident cancer[1]. According to recent statistics, presenting the estimated new cancer cases and deaths in the United States in 2024, around 26.500 new cases of gastric cancer and about 10.000 cases of estimated deaths were recorded[2]. Gastric cancer is the third most common cause of cancer mortality worldwide[1,3,4]. The incidence rate rises progressively with age with a median age at diagnosis is 70 years. However, approximately 10% of gastric carcinomas are detected at the age of 45 or younger[1].

Risk factors for the condition include *Helicobacter pylori* infection, age, dietary habits and methods of food preservation [5,6]. Improvements in understanding of the complexity of cancer biology have been instrumental in advancing cancer treatments. Oncogenic alterations have multiple effects, including increase in proliferative signaling, resistance to cell death, bypassing replicative limit, increase in genome instability[7]. Gastric cancer is mainly diagnosed histologically after endoscopic biopsy and staged using computer tomography, endoscopic ultrasound, positron emission tomography, and laparoscopy[8].

Locally advanced gastric cancer is treated with perioperative chemotherapy and adequate radical surgery including D2 lymphadenectomy for patients who are able to tolerate a triple cytotoxic drug regimen[9,10]. In locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma, perioperative 5-FU/Leucovorin/Oxaliplatin/Docetaxel regimen improved overall survival compared with perioperative epirubicin/cisplatin/fluorouracil or capecitabine [10,11].

Beyond therapeutic strategies, malnutrition in patients with diagnosed gastric neoplasm and its treatment strategies remain a common clinical matter and a debated issue.

Nutritional update

Fasting and malnutrition cause intestinal atrophy, immune barrier disruption and promotes bacterial translocation leading to higher postoperative complication rate and poor prognosis[12-14]. Total parenteral nutrition remains widely adopted in postoperative timing, should though be limited to those patients where no other nutritional supplementation is possible[15,16]. In the preoperative context, oral or enteral feeding is well established as the preferred method of nutritional support. Additionally, surgical strategies and postoperative management should account for the patient's nutritional profile[10,17-20].

On this theme different approaches are proposed between western and eastern countries. Enhanced recovery after surgery protocols for upper gastrointestinal (UpperGI) surgery recommend oral nutrition from the first postoperative day [21]. Japanese Guidelines suggest a delayed introduction of oral intake, with solid diet beginning from postoperative day 2 to 4[22]. Currently, diverse controversies regarding the real advantages of early oral nutrition exist in the current literature, with authors publishing no anastomotic leakage rate increased with early oral nutrition[23] and Japanese randomized control trials demonstrating no differences in hospital stay with delayed oral intake[24,25]. Surgical planning could also contribute reducing postoperative malnutrition. Recently, double tract reconstruction was described as a novel technique allowing in selected cases to avoid total gastrectomy with the aim of maintaining better long term nutritional outcomes[26].

Feeding jejunostomy

Malnutrition is an well known risk factor raising morbidity and mortality rates among UpperGI cancer patients[27-29]. The placement of a feeding jejunostomy tube at the time of gastrectomy offers supplementary nutritional access, which may serve to ensure enteral access for meeting caloric needs, particularly in anticipation of the significant gastrointestinal side effects during adjuvant therapy. In order to permit a patient to complete treatment, the National Comprehensive Cancer Network currently recommends that a placement of jejunostomy to be considered for patients receiving postoperative adjuvant therapy[30].

A study on patients undergoing an oesophagectomy for cancer, elaborated the question if immediate postoperative enteral feeding (*via* percutaneous jejunostomy or nasojejunostomy) provides better patient outcomes as compared to waiting until oral feeding can be instituted. Both methods were equally effective in providing postoperative nutrition. All included trials concluded that routine postoperative enteral nutrition was feasible, but there was no evidence suggesting

that it conferred any clinical benefits[31]. The retrospective study performed by Jaquet *et al*[20], demonstrated a significant positive impact of postoperative enteral nutrition *via* jejunostomy on some complications. Enterally fed patients had a decreased rate of infectious complications, respiratory complications and grade III complications according to the Dindo-Clavien classification. Additionally, the postoperative nutritional status was better in patients fed *via* jejunostomy, regarding weight loss and albumin decrease. To date there are no large-scale randomized clinical trials or meta-analyses available on the topic, nevertheless the indication to supplement malnourished patients by enteral nutrition in the perioperative period is established in several international guidelines[19,21,30]. A large United States retrospective multicentric study with primary outcome focused on rate of postoperative complications and completion of adjuvant therapy reported an increased rate of infectious complications including anastomotic leakage with no increased receipt of chemotherapy in patients undergoing gastrectomy and jejunostomy placement. Of 837 patients, 265 (32%) received a jejunostomy tube. Patients receiving a jejunostomy demonstrated greater incidence of preoperative weight loss, lower body mass index (BMI), greater extent of resection, and more advanced TNM stage. The jejunostomy placement was associated with increased infectious complications (36% *vs* 19%, $P < 0.001$), including surgical-site (14% *vs* 6%, $P < 0.001$) and deep intra-abdominal (11% *vs* 4%, $P < 0.001$) infections. Jejunostomy remained an independent risk factor even after multivariate analysis and subset analysis stratified by operation type (total and subtotal gastrectomy) [32]. Contrasting findings were reported in the propensity-matched analysis by Sun *et al*[33], which retrospectively examined a large cohort of patients undergoing gastrectomy and jejunostomy placement for cancer. The study found no significant increase in morbidity or mortality rates within 30 days, supporting early enteral nutrition as a safe clinical practice. One possible explanation is the significantly lower rate of intra-abdominal leaks following gastrectomy (approximately 1%), compared to the higher rates observed in esophagectomy (around 12%) and pancreaticoduodenectomy (about 13%). This difference may explain why a jejunostomy placement does not appear to elevate morbidity in gastrectomy patients[33]. Concerning the esophageal surgery field, there is little support by statistical data despite the diffuse feeding jejunostomies placement in the clinical routine. A summary of four different randomized control trials on the topic reported no differences in terms of anastomotic leakage and postoperative complications in patients receiving jejunostomy during radical surgery[31].

The decisional process and the correct indication become even more complex in the era of perioperative chemotherapy. Explorative laparoscopy is standardized in most staging workups regarding patients potentially eligible for perioperative multimodal treatment[34].

Jejunostomy placement during staging laparoscopy was proposed attempting to give nutritional support during the perioperative time. This technique results safe with no major complications despite a low rate of minor complications including catheter displacement, local cutaneous erosion, wound infection, pericatheter leak or occlusion with generalized peritonitis, aspiration pneumonia, small bowel necrosis, small bowel obstruction, pneumatosis intestinalis, abdominal wall infection, fistula and volvulus[35]. Currently few retrospective studies with small numbers report low complication rates deeming the technique safe; however, long-term data are lacking to establish a real benefit in terms of improved nutritional status, adjuvant therapy completion rate, and oncologic outcomes. Further studies are needed to validate the technique and standardize its use[35].

CONCLUSION

Enteral nutrition has many advantages over intravenous nutrition, including immune and intestinal mucosa support, avoidance of bacterial translocation, and decreased risk of venous catheter infection. The article "Benefits of jejunostomy feeding in patients who underwent gastrectomy for cancer treatment" by Jaquet *et al*[20] supports the placement of jejunostomy in gastric cancer patients showing fewer complication rates[20]. Patients obtaining jejunostomies had more often advanced tumors requiring a total gastrectomy, a longer hospital stay, lower BMI and a greater incidence of weight loss. This shows an evident selection bias, intrinsic in the retrospective design of the study which could possibly be mitigated by a propensity matched analysis. No differences in terms of anastomotic leak rate or long-term oncological outcomes were found, according to the current literature.

Especially in the West, due to the absence of screening protocols, gastric cancer is often late diagnosed with advanced local extension of disease. In this context, patients often present with severe malnutrition and sarcopenia related to mechanical (dysphagia, reduced caloric intake) and metabolic mechanisms. In the era of perioperative chemotherapy as the standard of care in the treatment of advanced gastric cancer, the debate regarding the advantages of jejunostomy placement for nutritional purposes during diagnostic exploratory laparoscopy or demolitive surgery is highly relevant. Further larger randomized controlled trials with standardized protocols and long-term follow-up studies are needed to confirm and validate these results.

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LETTER TO THE EDITOR

Current opinions on the use of prophylactic antibiotics in patients undergoing laparoscopic cholecystectomy

Efstathios T Pavlidis, Ioannis N Galanis, Theodoros E Pavlidis

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Abstract

Inappropriate use of antibiotics leads to microbial resistance. Single-dose antibiotic prophylaxis prior to laparoscopic cholecystectomy is well known for reducing the risk of postoperative infection in high-risk patients despite some conflicting aspects. High-risk patients are those who are older than 70 years, have diabetes mellitus, whose operation time exceeded 120 minutes, have acute cholecystitis, experienced iatrogenic intraoperative gallbladder perforation resulting in bile or gallstone spillage, suffered from obstructive jaundice, or were deemed immunocompromised. For gallbladder perforation, one dose of antibiotic prophylaxis is sufficient. Therefore, guidelines are needed and must be strictly followed. Prophylactic treatment is not needed for patients at low risk of developing sepsis following elective laparoscopic cholecystectomy, although the opposite is supported. Similarly, superficial surgical infections are related to low morbidity. Patients without risk factors have a very low risk of infection. Thus, the routine use of antibiotic prophylaxis in elective laparoscopic cholecystectomy is not recommended.

Key Words: Prophylactic antibiotics; Gallstone disease; Laparoscopic cholecystectomy; Acute cholecystitis; Skin incision infection; Septic complications

Core Tip: In the most cases of elective laparoscopic cholecystectomy, there is a low possibility of septic complication development and no need for prophylactic antibiotics. In few patients with some well-defined risk factors for infection, including acute cholecystitis, the antibiotic prophylaxis before skin incision is necessary to minimize such complications.

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TO THE EDITOR

Clinicians must be careful in deciding to administer antibiotics for prophylaxis, as there is a risk of microbial resistance in the event of excessive use or abuse. Microbial resistance has become a source of major concern worldwide, as new, more powerful, antibiotics are being discovered to treat severe infections refractory to previously effective treatment methods. Perioperative antibiotic prophylaxis has been used in patients scheduled for elective and emergency operative procedures [1]. Laparoscopic simple cholecystectomy for uncomplicated cholelithiasis is related to a very low risk of infection[2,3], since the bile entering the biliary tree is typically aseptic; however, impeded flow of bile is known to promote the growth of microbes, especially in patients of an advanced age[4,5]. Wang[6] recently published a retrospective study in the *World Journal of Gastrointestinal Surgery* evaluating the risk factors for surgical site infections and the effectiveness of prophylactic antibiotics in patients undergoing laparoscopic cholecystectomy and reported very interesting outcomes.

Single-dose intravenous antibiotic prophylaxis at the beginning of laparoscopic cholecystectomy is well known for preventing the risks of skin incision infections or other septic complications in high-risk patients[6,7-10], despite the existence of some conflicting aspects and the opposite supporting no antibiotic prophylaxis at all[11-15]. High-risk patients are those who are older than 70 years, have diabetes mellitus, whose surgery duration exceeded 120 minutes, were diagnosed with acute cholecystitis, suffered from iatrogenic intraoperative gallbladder perforation resulting in bile or gallstone spillage, experienced obstructive jaundice, and were deemed immunocompromised[6,7,15,16]. The timing, selection, and duration of perioperative antibiotic prophylaxis for skin wound infections are the determining factors[11,12]. However, guidelines are needed and strict adherence is required for all medical and nursing staff[17].

Antibiotic prophylaxis is not required for patients at low risk of developing sepsis after elective laparoscopic cholecystectomy; however, in addition to the most appropriate surgical technique, meticulous application of alternative infection prevention measures with antiseptic protocols and thorough preoperative preparation, is needed for such patients[18-22]. However, the opposite has been supported. The argument for the latter opinion is based on a meta-analysis that revealed a reduction in the incidence of surgical site infections and distant or overall infections after antibiotic prophylaxis[23].

In addition, superficial surgical infections such as skin incision infections are unlikely to lead to morbidity[24]. Therefore, patients without risk factors have a very low risk of infection and do not need prophylactic antibiotics[1,25,26].

The World Health Organization has general guidelines for the prevention of surgical site infections in patients undergoing any surgical procedure, particularly cardiothoracic and orthopedic procedures, mainly for *Staphylococcus aureus*, where beta-lactam antibiotics play a dominant role as well as other prophylactic measures[27]. Elective laparoscopic cholecystectomy has a low risk for such infection.

Strong evidence-based guidelines for laparoscopic cholecystectomy do not exist, and there is ongoing debate. The United States of America Surgical Infection Society recognizes the need for better evidence in guidelines focusing on the appropriate use of antibiotics in patients undergoing laparoscopic cholecystectomy. They recommend the following: (1) No routine perioperative prophylactic antibiotic use in patients undergoing elective operations, only selective use in high-risk cases; (2) No use for symptomatic cholelithiasis; (3) No use for mild or even moderate acute cholecystitis; and (4) Use only for severe inflammation according to the Tokyo classification for a maximum of 4 days[28].

Identifying any risk factor for infection is the first step in diagnosis[6]. Liver function tests (transaminases, bilirubin, alkaline phosphatase, and gamma-glutamyl transferase) are necessary before every cholecystectomy. Elevations in such markers indicate cholestasis, and gallstone disease found on biliary ultrasound warrant magnetic resonance cholangiopancreatography (MRCP)[29].

Gallbladder bile samples for culture obtained *via* paracentesis under imaging guidance can be helpful in the event that inflammation markers (white blood cell count, polymorphonuclear cell count, and c-reactive protein level) are elevated or that imaging is not possible, indicating acute gallbladder inflammation; however, there are practical challenges and limitations in routine clinical practice[4,5].

Elderly patients, patients with symptoms, and patients who undergo preoperative endoscopic retrograde cholangiopancreatography (ERCP) are more likely to have a positive bile culture[5].

In the case of concomitant common bile duct stones on MRCP, the recommendation is ERCP-endoscopic sphincterotomy and stone removal, followed by laparoscopic cholecystectomy[29], at which time antibiotic prophylaxis is necessary[5]. Bile culture-based antibiotics are more effective than empiric antibiotics after ERCP and in cases of acute cholecystitis[5,13].

Researchers have previously postulated that because antibiotic prophylaxis does not provide extra benefit for reducing the risk of postoperative infections and is not cost-effective, its use is not justified, even more so for patients with mild-to-moderate acute cholecystitis undergoing emergency laparoscopic cholecystectomy[12,17,30].

A comparative study revealed that cefazolin (2 g) before anesthesia for elective laparoscopic cholecystectomy in low-risk cases had no impact on the incidence of surgical site infection, with a ratio of 2% in both groups[31]. However, in patients with acute cholecystitis, a recent multicenter randomized controlled trial showed that 2 g of cefazolin before incision was associated with fewer postoperative infections (7.1%) than no antibiotic prophylaxis (12.6%), leading to its

undeniable recommendation[17,32].

Prophylactic antibiotics is required for older patients in any case[4]. Additionally, if the operation time is expected to be prolonged, a single dose of 2 g of cefazolin intravenously must be applied before the skin is incised[7].

The most preferred antibiotic for prophylaxis is cefazolin[3,4,18,20,32], a first-generation cephalosporin, but cefuroxime [33], a second-generation cephalosporin or even third-generation ceftriaxone, has also been used in cases of acute cholecystitis[8].

For iatrogenic intraoperative gallbladder perforation and spillage of bile or stones, a single dose of an antibiotic is sufficient, especially in combination with proper cleaning and local irrigation of the operative field[34-36].

Alternatives for patients with beta-lactam allergies or for those undergoing prolonged surgeries who are at risk of gram-negative infections constitute beta-lactamase inhibitors, *i.e.*, mainly among tazobactam (piperacillin with clavulanic acid), ampicillin with sulbactam, third-generation cephalosporins or carbapenems[37].

The routine use of antibiotic prophylaxis in patients scheduled to undergo elective laparoscopic cholecystectomy is not recommended, except in select patients at high risk of infection, including those scheduled for emergency laparoscopic cholecystectomy for mild to moderate acute cholecystitis.

FOOTNOTES

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LETTER TO THE EDITOR

Enhancing palliative care in malignant obstructive jaundice: A critical care perspective on endoscopic biliary stenting

Yun Xie, Hui Xie, Rui-Lan Wang

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Abstract

This letter responds to Wang *et al*'s recent publication on endoscopic biliary stenting for malignant obstructive jaundice (MOJ) by offering constructive feedback and suggestions for future research. We commend the authors for their comprehensive study design and execution, which included a clear delineation of study groups and a robust set of outcome measures. We suggest that future studies incorporate additional biomarkers, such as serum levels of liver enzymes and bilirubin, to provide a more nuanced understanding of liver function changes post-intervention. The study's focus on short-term survival rates is appreciated, but we recommend exploring longer-term follow-up periods to capture the full spectrum of survival outcomes. Additionally, the inclusion of quality of life assessments using validated instruments could offer a more holistic view of patient outcomes. From a critical care perspective, we advocate for the integration of advanced imaging techniques to better characterize biliary anatomy and potentially predict treatment response or complications. We believe that incorporating these suggestions could enhance the understanding of endoscopic biliary stenting's role in MOJ management and its impact on patient outcomes, influencing future clinical guidelines and practice.

Key Words: Malignant obstructive jaundice; Endoscopic biliary stenting; Palliative care; Critical care; Liver function; Quality of life

Core Tip: The core tip of the manuscript is to evaluate the efficacy of endoscopic biliary stenting for malignant obstructive jaundice and compare it with the standard palliative approach, percutaneous transhepatic biliary drainage. The study suggests incorporating additional biomarkers for a nuanced understanding of liver function changes and emphasizes the importance of long-term follow-up to assess survival outcomes and the durability of palliative effects. It also highlights the need for quality of life assessments and advanced imaging techniques to predict treatment response and complications, contributing to a more holistic view of patient outcomes.

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TO THE EDITOR

We recently read an interesting article titled "Clinical evaluation of endoscopic biliary stenting in treatment of malignant obstructive jaundice" by Wang *et al*[1], published in the *World Journal of Gastrointestinal Surgery*. This retrospective study provides valuable insights into the efficacy of endoscopic biliary stenting for treating malignant obstructive jaundice (MOJ) and offers a comparative analysis with percutaneous transhepatic biliary drainage (PTBD), a standard palliative approach. The most common causes of MOJ are pancreatic cancer and cholangiocarcinoma (primary cholangiocarcinoma or bile duct cell carcinoma). Let us take cholangiocarcinoma as an example. In the Surveillance, Epidemiology, and End Results (SEER) database, of 8584 cases of cholangiocarcinoma, 48.4% (n = 4157) were in women (Figure 1A), 54.7% (n = 4698) were in individuals aged 60-79 years (Figure 1B), 62.5% (n = 5362) were treated nonsurgically (Figure 1C), 15.9% (n = 1370) were treated surgically, 14.1% (n = 1214) were treated with radiotherapy (Figure 1D), of which beam radiation was the main treatment (n = 903), and 39% (n = 3374) were treated with chemotherapy (Figure 1E). Unfortunately, PTBD data were not recorded. We thank the authors for their thorough investigation and appreciate the potential implications for clinical practice in the management of MOJ. However, we would like to offer some constructive feedback and suggestions for future research on this topic.

First, the study was well designed and appropriately executed, with a clear delineation of the study groups and a comprehensive set of outcome measures. The use of liver function indices to assess the impact of interventions is a robust methodological choice. However, we suggest that future studies might benefit from incorporating additional biomarkers, such as serum levels of liver enzymes and bilirubin, to provide a more nuanced understanding of post-intervention changes in liver function[2].

Second, while the study provides a comparison of 3-year survival rates, a lack of statistical significance between the groups is noted. Our study revealed that 13% of cholangiocarcinoma patients in the SEER database survived for more than three years (Figure 1F). Future studies should include longer-term follow-up periods to capture the full spectrum of survival outcomes and to better understand the durability of the palliative effects of endoscopic biliary stenting.

Third, the study's focus on complications and adverse events is crucial, given the palliative nature of the treatment. However, the inclusion of quality of life assessments, using validated instruments such as the EQ-5D or the Liverpool-Pediatric Quality of Life, could offer a more holistic view of patient outcomes and the impact of the treatment on daily functioning and well-being. From a critical care perspective, Endoscopic biliary stenting effectively alleviates cholangial injury and obstruction in the palliative treatment of MOJ, reducing the incidence of acute suppurative obstructive cholangitis and thereby lowering the risk of infections and complications in the intensive care unit. By relieving biliary obstruction and mitigating or eliminating jaundice, this procedure improves patients' overall condition, decreasing the likelihood of common critical care issues such as electrolyte and acid-base imbalances caused by biliary obstruction, and providing a more stable physiological state. Postoperative care for endoscopic biliary stenting is crucial in the intensive care setting, with medical staff needing to closely monitor patients' vital signs and drainage status, promptly addressing potential complications like stent blockage or displacement to ensure patient safety and treatment efficacy. We also suggest that future research should consider the integration of advanced imaging techniques, such as cross-sectional imaging or cholangiography[3], to better characterize the biliary anatomy and potentially predict the response to treatment or the risk of complications.

There are several areas that could benefit from further expansion or clarification: (1) Discussion on other treatment modalities: The review could benefit from a brief mention of alternative palliative treatments for MOJ, such as newer stent technologies or intrahepatic biliary drainage. This would provide a broader view of the available therapeutic options and their potential advantages over endoscopic biliary stenting; (2) Statistical analysis: It would be helpful to include a more detailed critique of the statistical methods used in the original study, particularly in regard to survival analysis. Discussing specific statistical tests or models, such as Kaplan-Meier survival curves or Cox regression, would further enrich the review; and (3) Personalized treatment approaches: A mention of how patient-specific factors (*e.g.*, cancer stage, comorbidities, age) could influence the choice of palliative treatment might add depth to the review. Personalization is a growing focus in medicine, and this aspect could be particularly relevant in the context of managing MOJ.

In conclusion, the study by Wang *et al*[1] contributes significantly to the body of knowledge on palliative care options for MOJ. We believe that the incorporation of our suggestions could further enhance the understanding of the role of

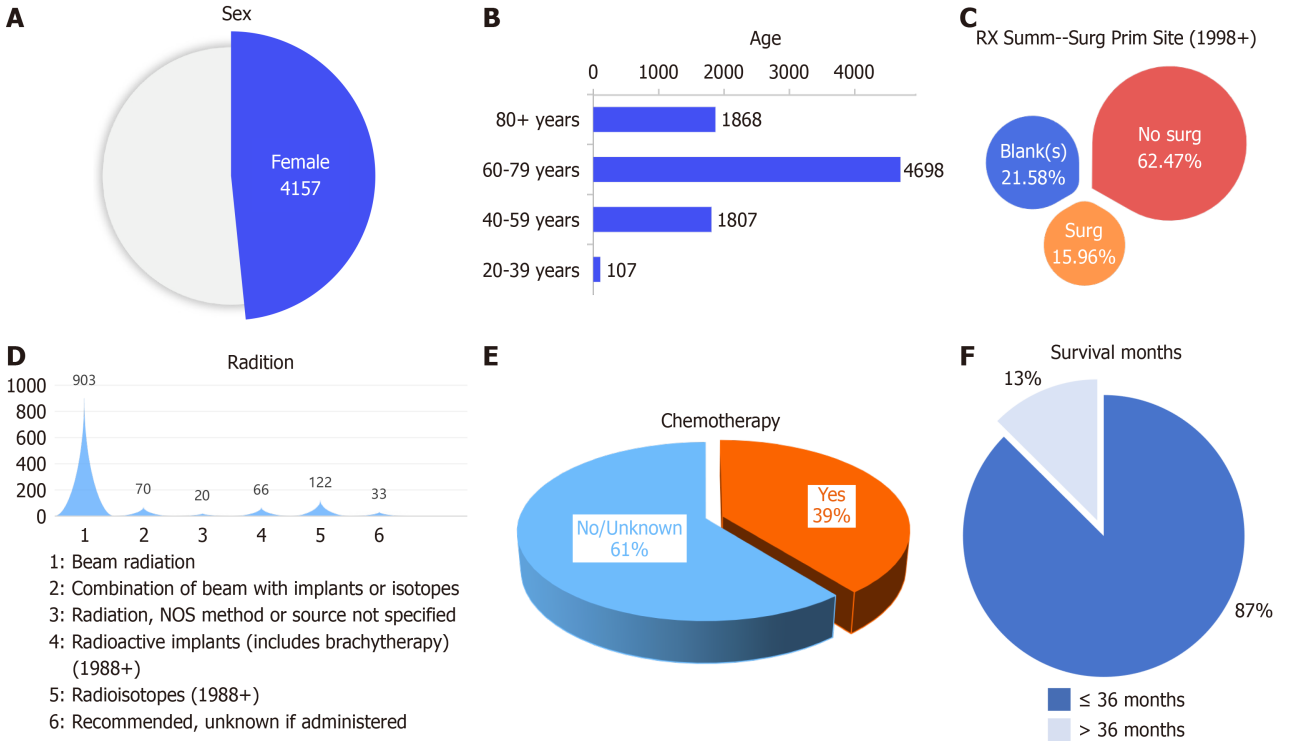

Figure 1 A research on cholangiocarcinoma, data were extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results program. A: Sex of the study population, which indicates the gender distribution among the participants; B: Age of the study population, detailing the age range and distribution of the individuals involved; C: Surgical information, encompassing the types and prevalence of surgical procedures performed; D: Radiation record, documenting the types of radiation therapies administered; E: Chemotherapy record, outlining the chemotherapy regimens utilized; F: Survival months, showcasing the duration of survival post-diagnosis or treatment for the patients in the study. NOS: Not otherwise specified.

endoscopic biliary stenting in the management of MOJ and its impact on patient outcomes. We look forward to witnessing how this research evolves and how it might influence clinical guidelines and practice.

FOOTNOTES

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