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AIMS AND SCOPE

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

Pan-immune-inflammation in colon cancer: A prognostic biomarker and the role of tumor location in personalized care

Gaya Spolverato, Giulia Capelli, Floriane Noel, Michele Steindler, Andrew Alexander Gumbs

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Abstract

Despite advances in surgery, chemotherapy, and radiotherapy, the treatment of colorectal cancer (CRC) requires more personalized approaches based on tumor biology and molecular profiling. While some relevant mutations have been associated with differential response to immunotherapy, such as *RAS* and *BRAF* mutations limiting response to anti-epithelial growth factor receptor drugs or microsatellite instability predisposing susceptibility to immune checkpoint inhibitors, the role of inflammation in dictating tumor progression and treatment response is still under investigation. Several inflammatory biomarkers have been identified to guide patient prognosis. These include the neutrophil-lymphocyte ratio, Glasgow prognostic score (GPS) and its modified version, lymphocyte-C-reactive protein ratio, and platelet-lymphocyte ratio. However, these markers are not yet included in the standard clinical management of patients with CRC, and further research is needed to evaluate their efficacy in different patient populations. A recent study by Wang *et al*, published in the *World Journal of Gastroenterology*, sheds light on the prognostic significance of pan-immune-inflammation value (PIV) in CRC, particularly concerning primary tumor location. Specifically, the authors found that a high PIV was strongly correlated with worse disease-free survival in patients with left-sided colon cancer, whereas no such association was observed in patients with right-sided colon cancer. Integrating tumor location into the prognostic assessment of CRC may improve our ability to more accurately

identify high-risk patients and develop personalized treatment plans that are more likely to improve patient outcomes.

Key Words: Colorectal cancer; Inflammatory biomarkers; Tumor location; Targeted therapy

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Core Tip: A recent study by Wang *et al* highlights that a high pan-immune inflammation value is associated with worse disease-free survival in left-sided colon cancer, but not in right-sided colon cancer. This suggests that considering tumor location in colorectal cancer prognosis may help identify high-risk patients and more effectively tailor treatment plans.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and a leading cause of cancer-related deaths[1]. Despite advances in surgery, chemotherapy, and radiotherapy, the limitations of these treatments underscore the urgent need for more personalized approaches[2]. Biomarkers, biological molecules that hold the key to unlocking a new era of precision in CRC care, are emerging as critical tools in this regard[3,4].

BIOMARKERS: A NEW ERA OF PRECISION IN CRC

Molecular profiling: Unmasking the tumor's identity

Genetic and epigenetic alterations drive the development and progression of CRC. Unraveling the unique molecular profile of the tumor through biomarker analysis is critical for guiding treatment decisions, particularly in advanced or metastatic disease[3]. In particular, the mutational profile of the tumor can predict the response to epithelial growth factor receptor (EGFR)-targeting monoclonal antibodies, such as cetuximab and panitumumab, which have been validated over the past 20 years as powerful tools for prolonging survival in patients with metastatic CRC[5].

Key players in this molecular landscape include RAS mutations (*KRAS*, *NRAS*) and *BRAF* mutations, particularly the *V600E* mutation, which confer resistance to anti-EGFR therapies and are associated with poorer prognosis[3,6,7]. Similarly, human epidermal growth factor receptor 2 (HER2) amplification, although relatively rare in CRC, can drive tumor growth and predict resistance to anti-EGFR therapies. However, anti-HER2 therapies, initially successful in treating HER2-positive breast cancer, are now showing promise in HER2-amplified metastatic CRC[3,8]. Finally, microsatellite instability-high (MSI-H) tumors have a distinct molecular profile characterized by a high number of mutations and neoantigens, making them particularly susceptible to immune checkpoint inhibitors (ICIs), a major breakthrough in CRC treatment[9]. These drugs, which block inhibitory signals that suppress the immune system, have demonstrated remarkable efficacy in patients with MSI-H/dMMR CRC, resulting in durable responses and improved survival[9,10]. Unfortunately, the majority of CRC tumors are microsatellite stable or mismatch repair proficient, rendering them less responsive to ICIs[11]. This is largely due to their lower tumor mutational burden and weaker immunogenicity, making them adept at evading immune surveillance[9,12]. Overcoming this immune evasion is a major focus of ongoing research, with strategies exploring combinations of ICIs with other treatment modalities, such as chemotherapy, targeted therapies, and radiotherapy[9,12].

Inflammation: A silent partner in CRC progression

Chronic inflammation plays a critical role in the development and progression of CRC, influencing tumor growth, angiogenesis, and metastasis[2]. In recent years, several studies have linked inflammation to postoperative recurrence in patients undergoing curative surgery for CRC. For example, Matsubara *et al*[13] found that high post-resection C-reactive protein (CRP) levels were linked to significantly worse recurrence-free survival in 467 patients with stage I–III CRC who underwent curative surgery. Similarly, Di Caro *et al*[14] discovered that high preoperative serum levels of inflammatory cytokines and the acute-phase protein Pentraxin-3 were associated with an increased risk of recurrence independently of TNM staging in 69 patients. Consequently, several inflammation-related biomarkers, readily available through routine blood tests, have emerged as valuable prognostic indicators[2]. Elevated neutrophil-lymphocyte ratio, reflecting a higher proportion of neutrophils to lymphocytes, is consistently associated with poorer prognosis in CRC[2,4,15]. The Glasgow prognostic score and its modified version incorporate serum CRP and albumin levels, reflecting both systemic inflammation and nutritional status, with higher scores linked to worse outcomes[2,4,16]. A low lymphocyte-CRP ratio,

indicating a lower proportion of lymphocytes to CRP, is associated with poorer prognosis and increased risk of postoperative complications[2,17]. Elevated platelet-lymphocyte ratio, reflecting a higher proportion of platelets to lymphocytes, is linked to poorer prognosis in CRC, particularly in advanced stages[2,18]. While these biomarkers hold significant promise, their optimal cutoff values and clinical application remain areas of active investigation. Multicenter prospective studies are crucial to standardize their use and maximize their clinical utility[2].

The crucial role of inflammation in CRC should also be viewed as a driver of oncogenic mutations. For example, KRAS mutations are more commonly present in CRC arising from chronic inflammatory disease. Conversely, these mutations have been shown to create an immunosuppressive tumor microenvironment (TME), suppressing the expression of pro-inflammatory cytokines. Therefore, there is a complex and yet unclear link between chronic inflammation, the development[19] of oncogenic mutations, and the immunomodulation of the TME. Understanding this intricate relationship may lead to many interesting developments in personalized therapy in the next few years.

PAN-IMMUNE-INFLAMMATION VALUE AS A LOCATION-SPECIFIC BIOMARKER

A recent study by Wang *et al*[20], published in the *World Journal of Gastroenterology*, sheds light on the prognostic significance of the pan-immune-inflammation value (PIV) in colon cancer, particularly in relation to primary tumor location. This research is a pivotal contribution to our understanding of the complex interactions between systemic inflammation and tumor biology in CRC.

The distinction between left-sided colon cancer (LCC) and right-sided colon cancer (RCC) has been well established, with each subtype exhibiting distinct clinical, pathological, and molecular characteristics[21]. The study by Wang *et al*[20] adds to this narrative by demonstrating that the prognostic utility of PIV is significantly influenced by tumor location within the colon. Specifically, the authors found that a high PIV was strongly correlated with poorer disease-free survival in patients with LCC, whereas no such association was observed in patients with RCC.

The implications of these results are profound, suggesting that the prognostic value of systemic inflammatory response markers, such as PIV, may not be universally applicable across all colon cancer subtypes. Instead, the efficacy of these biomarkers may vary depending on tumor location, necessitating a more nuanced approach to their clinical application. In patients with LCC, a high PIV could serve as a critical indicator of poor prognosis and guide more aggressive and tailored treatment strategies. Conversely, the lack of a significant correlation between PIV and disease-free survival in patients with RCC highlights the need for further research to identify more relevant prognostic markers for this subgroup.

The uncertainty surrounding the prognostic value of PIV in RCC may be attributed to the distinct characteristics of the TME inherent to tumor location. RCCs exhibit a higher prevalence of *KRAS* and *BRAF* mutations. In contrast, TP53 mutations are more frequently observed in LCC. These genetic alterations contribute to an immunosuppressive TME, influencing tumor behavior and patient outcomes.

Furthermore, MSI-H tumors, which are more prevalent in RCC, exhibit an augmented inflammatory response and an enhanced recognition by the immune system, rendering them more responsive to immunotherapy. Consequently, elevated circulating inflammatory biomarkers may potentially predict a patient's response to treatment. In rectal cancer, increased neutrophil-lymphocyte ratio and platelet-lymphocyte ratio before neoadjuvant chemoradiotherapy have been linked to poorer prognosis in patients with MSI-H. While this correlation has yet to be demonstrated in patients with colon cancer, it presents promising avenues for future research. Therefore, genetic, molecular, and inflammation-related characteristics should be considered when designing personalized therapies for patients with CRC. Further investigation is warranted to elucidate the relationship between inflammation and TME characteristics across different tumor locations and to understand the potential prognostic roles of inflammatory markers in CRC[22-24].

The large sample size and rigorous methodology of the study by Wang *et al*[20] lend credibility to its conclusions and strongly support integrating tumor location into the prognostic assessment of colon cancer. This integration could improve our ability to more accurately identify high-risk patients and develop personalized treatment plans that are more likely to improve patient outcomes. However, the study also raises important questions about the underlying mechanisms driving the observed differences in the prognostic value of PIV between LCC and RCC. The role of various immune and inflammatory cells in the TME, as well as their interaction with tumor cells, may differ significantly between these subtypes, influencing the overall prognostic landscape. The role of TME in influencing tumor behavior has already been studied in rectal cancer, particularly in relation to response to neoadjuvant treatment, and immunological and molecular differences in different populations have been associated with different prognoses[25,26]. Further research is needed to elucidate these mechanisms and to explore whether other systemic inflammatory response markers may also have site-specific prognostic value.

Furthermore, it should be noted that the study by Wang *et al*[20] is not without limitations, as acknowledged by the authors themselves. Notably, the absence of data on molecular mutations—specifically RAS mutations—and the lack of information regarding adjuvant therapy limit the applicability of their results. These gaps highlight the need for further research to validate and expand upon their findings.

FUTURE DIRECTIONS: TOWARDS A CONTINUUM OF PERSONALIZED CARE

Recent studies have highlighted the crucial function of inflammation in the genesis and recurrence of colon cancer, prompting a shift toward the investigation of novel targets for systemic therapy. Preclinical models have demonstrated

encouraging outcomes with agents such as JAK inhibitors, chemokine receptor antagonists (*e.g.*, CXCR2 inhibitors), antibodies targeting the interleukin-6 receptor or its signaling pathway, and cyclooxygenase-2 inhibitors[27]. The integration of these therapeutic modalities with chemotherapy and surgical interventions holds considerable potential to significantly improve the prognosis of patients with colon cancer.

The future of CRC care lies in a comprehensive, multiomics approach that integrates data from genomics, transcriptomics, proteomics, and metagenomics to create a holistic picture of the tumor and its microenvironment[3,28]. Liquid biopsies, which analyze circulating tumor DNA, offer the potential for real-time monitoring of tumor evolution and treatment response, further refining personalized treatment strategies[3,29]. The integration of artificial intelligence could enhance the clinical application of whole-genome sequencing analysis, enabling more precise therapeutic decision-making and improving patient prognosis[30].

CONCLUSION

The study by Wang *et al*[20] represents a significant advancement in our understanding of the role of PIV as a prognostic biomarker in CRC. By highlighting the importance of tumor location, this research paves the way for more precise and personalized approaches to CRC treatment. As we continue to explore the molecular and inflammatory landscape of CRC, the integration of such biomarkers into clinical practice will be critical to improving patient outcomes and advancing the field of precision medicine in oncology.

Biomarkers are changing the landscape of CRC care, shifting the focus beyond the limitations of traditional approaches toward a future of precision medicine. By unlocking the molecular secrets of the tumor and harnessing the power of the immune system, we can tailor treatment strategies to individual patients, maximizing their chances of survival and improving their quality of life. As the field advances, the integration of studies like Wang *et al*'s will be critical to refining and expanding our arsenal of prognostic tools, ultimately improving patient care and outcomes[20].

FOOTNOTES

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EDITORIAL

Brief insight regarding the use of transanal, laparoscopic, and robotic total mesorectal excision for rectal cancer

Kevan English

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Abstract

In this article, we provide an important commentary on the original study Lu *et al*, which offers insight into the surgical efficacy of transanal total mesorectal excision (TaTME) *vs* laparoscopic total mesorectal excision (LapTME) in the management of low-lying locally advanced rectal cancer (LARC). We focus specifically on the rate of postoperative complications between the two using existing data from the literature. We additionally introduce robotic total mesorectal excision (RTME) and look at its postoperative complications relative to the TaTME and LapTME. LARC has been conventionally approached by open surgery. However, minimally invasive techniques have emerged over the past two decades as alternatives to open total mesorectal excision, namely robotic, laparoscopic, and transanal. Each approach has its supporters, but conflicting data on resection outcomes and complications has fueled ongoing debate over the optimal minimally invasive technique for low/mid-LARC. This article aims to extend on the data regarding the use of TaTME and RTME in the treatment of low/mid-LARC and further elaborate on their comparative efficacy relative to LapTME.

Key Words: Colorectal cancer; Total mesorectal excision; Laparoscopic excision; Surgical techniques; Surgical outcomes

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Core Tip: Total mesorectal excision (TME) is the standard of treatment for patients with low/mid locally advanced rectal cancer. This article compares the three minimally invasive surgical approaches (robotic, transanal, and laparoscopic TME) and their comparative efficacy relative to each other using the existing data in the literature.

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INTRODUCTION

Colorectal cancer (CRC) is a frequently diagnosed malignancy and the third most deadly cancer worldwide[1]. CRC incidence has been steadily increasing globally, particularly in developing countries that have adopted the Western way of life[1,2]. Obesity, high red meat consumption, sedentary lifestyle, tobacco use, and alcohol are significant risk factors for the malignancy[1-3]. Despite simultaneously evolving medical treatment with its rising incidence, surgical resection remains the standard approach for patients with rectal carcinoma[3,4]. Total mesorectal excision (TME) is the first-line surgical technique[5]. Open TME was conventionally performed in the mid-1980s; however, minimally invasive techniques have emerged as alternatives over the past two decades[5-7]. These include robotic, laparoscopic, and transanal TME for rectal cancer. There are supporters for each of these techniques in the medical community. However, conflicting evidence regarding specimen quality and complication rate has generated discussions regarding the optimal approach for low/mid locally advanced rectal cancer (LARC). This article aims to provide data from the existing literature, which suggests that both transanal TME (TaTME) and robotic TME (RTME) are preferred surgical approaches compared to laparoscopic (LapTME) for patients with low/mid-LARC.

EXISITING LITERATURE ON TME FOR TREATMENT OF LOW/MID-LARC

The retrospective study by Lu *et al*[8] which compared the efficacy of LapTME to TaTME, included a total of 94 patients with low-lying LARC who underwent minimally invasive surgery at a local hospital in China between 2022 and 2024[8]. The patients were selected and divided into TaTME (n = 50) and LapTME (n = 44) groups. Primary outcomes were anal function recovery, levels of surgical stress response, surgery-related indicators, surgical specimens, complication rate, visual analogue score after surgery, and quality of life. Results from the study showed that TaTME, when compared to LapTME, improved anal function, accelerated postoperative recovery, and reduced postoperative stress, showing it to be safer for patients with LARC. Although complication rates between the two (Table 1) were similar, the quality of resection specimens (Table 2) was higher among the TaTME group, contributing to a quicker postoperative recovery.

Another retrospective study by de'Angelis *et al*[9] compared the efficacy of all three minimally invasive surgical approaches using the European magnetic resonance imaging (MRI) and Rectal Cancer Surgery III database in patients who underwent TME between 2013 and 2022. A total of 468 patients were included, where 190 (40.6%) received LapTME, 141 (30.1%) received RTME, and 137 (29.3%) patients received TaTME. The primary outcome was the complication rate. Secondary outcomes included overall survival, disease-free survival, intraoperative variables (*i.e.*, blood loss, operating time, conversion rate), postoperative variables (*i.e.*, length of hospital stay), and quality of surgical resection. Comparative analysis after matching propensity score showed an elevated rate of postoperative complications for LapTME compared to both TaTME [odds ratio (OR) 2.87, 95%CI: 1.72-4.80] and RTME (OR 1.80, 95%CI: 1.11-2.91). TaTME (0.7%) and RTME (1.4%) were both correlated with smaller conversion rates to open surgery when juxtapose to LapTME (8.8%, $P < 0.001$). RTME was associated with a smaller rate of anastomotic leakage (grade A) (2%) compared to both LapTME (8.8%) and TaTME (8.1%, $P = 0.031$). Duration of hospital stay and time to flatus were briefer for patients treated with TaTME (P = 0.001 and 0.003, respectively).

No differences were observed in blood loss, operative time, mortality, intraoperative complications, R0 resection, survival, and readmission. This multicenter cohort study demonstrated that TaTME and RTME improved surgical outcomes in patients with low/mid-LARC compared to LapTME.

DISCUSSION

With the vagueness of the existing literature, this article adds to the existing data, suggesting that the newer minimally invasive techniques (RTME and TaTME) are better treatment options than LapTME for patients with low/mid-LARC. A relatively large cohort study by de'Angelis *et al*[9] showed that LapTME correlated with higher conversion rates to open surgery, reduced rate of stoma closure, and a higher incidence of postoperative complications compared to both TaTME and RTME. A meta-analysis by Lo Bianco *et al*[10] demonstrated that TaTME resulted in shorter hospitalizations, high-quality LARC operation, a lower percentage of tumor-positive margins, and a lower incidence of anastomotic complication such as leakage compared to LapTME.

Despite the evidence, LapTME remains the most common minimally invasive approach for LARC[9,11]. A nationwide study in Denmark showed that 48% of all TMEs were done laparoscopically, compared to 29.8% robotically and 13% transanally[12]. This widespread adoption is most likely due to early introduction that stuck within the surgery community, mainly related to surgeon's preferences and experience[9,13]. The increased use of LapTME is also seen globally compared to TaTME and RTME. It is important to note that the laparoscopic technique is highly challenging and requires

Table 1 Comparison of complications modified, *n* (%)

Groups	LapTME (*n* = 44)	TaTME (*n* = 50)	*P* value
Anastomotic fistula	1 (2.27)	1 (2.00)	
Anastomotic bleeding	3 (6.82)	2 (4.00)	
Ileus	3 (6.82)	2 (4.00)	
Incision infection	1 (2.27)	0 (0.00)	
Total occurrence	8 (18.18)	5 (10.00)	0.252

Comparison of complications modified from Lu *et al*[8]. LapTME: Laparoscopic total mesorectal excision; TaTME: Transanal total mesorectal excision.

Table 2 Comparison of resection specimens modified

Groups	LapTME (*n* = 44)	TaTME (*n* = 50)	*T* value	*P* value
Distal incisal margin (cm)	2.90 ± 0.78	3.40 ± 0.57	3.577	< 0.001
Specimen length (mm)	10.45 ± 2.37	12.12 ± 2.27	3.486	< 0.001
Total number of lymph nodes cleared (*n*)	11.18 ± 3.22	11.72 ± 3.26	0.806	0.422

Comparison of resection specimens modified from Lu *et al*[8]. LapTME: Laparoscopic total mesorectal excision; TaTME: Transanal total mesorectal.

skilled surgeons. TaTME and RTME have emerged as valuable alternative options to bypass technical limitations of LapTME and produce better surgical outcomes[8,12-14].

RECENT ADVANCES IN RESEARCH

Several trials, such as the COREAN studies and the MRC-CLASSICA, demonstrated no significant difference between LapTME and open surgery with respect to disease-free survival rates and local recurrence, ultimately favoring the efficacy and safety of laparoscopy in managing LARC in certain patients[15,16]. However, contemporary studies, namely ALaCaRT and ACOSOG Z6051, have failed to show the non-inferiority of laparoscopy compared to open surgery with respect to morbid outcomes, raising questions regarding oncologic safety of LapTME in the treatment of LARC[17,18].

RTME and TaTME were launched as alternative approaches to reduce the technical challenges of LapTME while maintaining high-quality oncologic outcomes. Recent meta-analyses based on several retrospective studies and one randomized controlled trial demonstrated similar results concerning oncologic and postoperative outcomes of TaTME compared with LapTME[19-21].

CONCLUSION

The newer minimally invasive techniques, including RTME and TaTME, have been shown to improve surgical outcomes compared to LapTME in treating low/mid-LARC. However, laparoscopy still dominates in the surgical community due to physician preference and experience. The existing literature suggests that RTME and TaTME are, in fact, both better and suitable alternatives to LapTME as they possess better postoperative outcomes.

FOOTNOTES

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MINIREVIEWS

Transjugular intrahepatic portosystemic shunt and non-selective beta-blockers act as friends or foe in decompensated cirrhosis: A comparative review

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Abstract

The management of portal hypertension and its complications, such as variceal bleeding, in patients with cirrhosis often involves the use of nonselective beta-blockers (NSBBs) and a transjugular intrahepatic portosystemic shunt (TIPS). Both treatment modalities have demonstrated efficacy; however, each presents distinct challenges and benefits. NSBBs, including propranolol, nadolol, and carvedilol, effectively reduce portal pressure, but are associated with side effects such as bradycardia, hypotension, fatigue, and respiratory issues. Additionally, NSBBs can exacerbate conditions such as refractory ascites, hepatorenal syndrome, and hepatic encephalopathy. In contrast, TIPS effectively reduces the incidence of variceal rebleeding, controlling refractory ascites. However, it is associated with a significant risk of hepatic encephalopathy, shunt dysfunction, and procedure-related complications including bleeding and infection. The high cost of TIPS, along with the need for regular follow-up and potential re-intervention, poses additional challenges. Furthermore, patient selection for TIPS is critical, as inappropriate candidates may experience suboptimal outcomes. Future studies comparing NSBBs and TIPS should focus on refining the patient selection criteria, enhancing procedural techniques, optimising combination therapies, and conducting long-term outcome studies. Personalised treatment approaches, cost-effectiveness analyses, and improved patient education and support are essential for maximising the use of these therapies.

Key Words: Transjugular intrahepatic portosystemic shunt; Liver cirrhosis; Variceal bleeding; Nonselective beta-blockers; Portal hypertension

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Core Tip: The management of portal hypertension in decompensated cirrhosis often involves nonselective beta-blockers (NSBBs) and a transjugular intrahepatic portosystemic shunt (TIPS). Although NSBBs effectively reduce portal pressure and prevent variceal bleeding, they can cause significant side effects, negatively impacting adherence. Conversely, TIPS provides rapid relief from variceal bleeding but carries risks such as hepatic encephalopathy and other complications. However, both treatments require careful patient selection and monitoring. Future strategies should focus on optimising patient management, enhancing procedural techniques, and integrating personalised approaches to improve outcomes in patients with cirrhosis.

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INTRODUCTION

Decompensated cirrhosis is a critical stage of liver disease, characterised by acute deterioration of hepatic function and the onset of life-threatening complications such as variceal bleeding, ascites, hepatic encephalopathy, and hepatorenal syndrome (HRS)[1,2]. According to Kim *et al*[1], this disease often results in the death of at least 85% of patients who do not receive a liver transplant within the first five years after presentation. Portal hypertension, a hallmark of decompensated cirrhosis, is a major driver of these complications, with an elevated portal pressure leading to variceal bleeding and other severe sequelae[2,3]. Notably, Garcia-Tsao[3] posited that the median survival rate of patients diagnosed with portal hypertension in decompensated cirrhosis was < 24 months.

The management of portal hypertension and its complications remains a significant challenge in clinical practice. Nonetheless, several treatment options are available, which vary across surgical procedures, such as the insertion of the transjugular intrahepatic portosystemic shunt (TIPS)[4]; medication regimens including the use of diuretics, lactulose, and rifaximin; and nonselective beta-blockers (NSBBs) such as propranolol[5], endoscopic band ligation, and liver transplantation. However, one of the most straightforward interventions involves lifestyle changes in terms of dietary intervention, weight moderation, and ultimately, cessation of alcohol consumption[6].

NSBBs, such as propranolol and carvedilol, have long been established as first-line therapies for reducing portal pressure and preventing variceal bleeding[7]. These medications decrease cardiac output and induce splanchnic vasoconstriction, thereby reducing portal venous pressure. However, their use is often limited by the significant side effects associated with NSBBs, including bradycardia, hypotension, and exacerbation of conditions such as refractory ascites and hepatic encephalopathy. NSBB therapy adherence is further complicated by the need for lifelong treatment and regular monitoring[8].

In contrast, TIPS offers a more invasive but effective approach for managing portal hypertension by creating a shunt between the portal and hepatic veins, thereby reducing portal pressure[9,10]. While TIPS is highly effective in controlling variceal bleeding and refractory ascites, it is associated with risks such as hepatic encephalopathy, shunt dysfunction, and procedure-related complications[10]. The high cost of TIPS, along with the need for specialised expertise and ongoing follow-up, further complicate its use.

Despite the widespread use of both NSBBs and TIPS, there is a lack of consensus regarding the optimal approach for managing portal hypertension in decompensated cirrhosis[11,12]. The choice between these therapies often depends on patient-specific factors, including the severity of liver disease, presence of comorbidities, and the risk of complications. Moreover, the comparative efficacy, safety, and long-term outcomes of NSBBs and TIPS have not yet been fully elucidated, particularly in the context of modern advancements in both pharmacological and interventional therapies.

This study aimed to provide a comprehensive comparative review of NSBBs and TIPS in the management of decompensated cirrhosis, focusing on their mechanisms of action, efficacy, safety profiles, and challenges in clinical practice. By analysing the latest evidence, we sought to clarify the roles of these therapies in different clinical scenarios and highlight the areas where further research is required to optimise patient outcomes. This study also reviews the mechanisms and indications of NSBBs and TIPS, followed by a comparative analysis of their efficacy and complications. Finally, we discuss future research directions, including the potential for personalised treatment approaches and the integration of emerging therapies.

NSBBS

Following the discovery of propranolol more than three decades ago, NSBBs have emerged as a crucial first-line intervention therapy for the management of decompensated cirrhosis. Several randomised control trials (RCTs) have demonstrated significantly positive outcomes for the efficacy of NSBBs in preventing both primary and secondary bleeding episodes from esophagogastric and portal hypertensive gastropathy[13-16]. Moreover, the administration of NSBBs in patients with cirrhosis has been associated with reduced bacterial translocation, reduced spontaneous bacterial peritonitis, and increased overall survival, independent of bleeding events[17,18].

The primary mechanism of NSBBs relies on their ability to affect beta-1 and beta-2 receptors in the myocardium and splanchnic vascular beds, respectively[19]. Through alterations in the beta-1 receptors, NSBBs can significantly decrease cardiac output and contractility. In contrast, beta-2 receptors, in turn, can cause vasoconstriction of the portal veins, primarily due to the unopposed activity of alpha-1 adrenergic receptors in the splanchnic vascular bed, resulting in a net reduction in the portal vein[19]. As indicated earlier, intrahepatic vascular resistance caused by distortions in hepatic anatomy is the primary cause of portal hypertension. Bhathal and Grossman[20] posited that almost 40 percent of this resistance could be functionally reversed by manipulating the specific locations of contractile elements found in the hepatic vascular landscape, thus modulating portal hypertension.

Recent studies have highlighted the abundance of alpha-1 adrenergic receptors in the systemic and splanchnic vascular anatomy of smooth muscles across the genitourinary tract. Thus, Al-Ghamdi[19] analysed the hypothesis that antagonisation of these receptors could reduce intrahepatic vascular tone and attenuate portal pressure. A subsequent trial by Albillos *et al*[21] involving the administration of propranolol combined with prazosin, an established alpha-1 blocker, in 28 patients compared with the administration of propranolol in addition to isosorbide-5-mononitrate in a 28-member cohort for three months showed a more significant reduction in the hepatic venous pressure gradient in the former than in the latter. However, this cohort was also associated with more hypotensive events and lower tolerance than the latter [21].

Thus, carvedilol, an NSBB composed of a mixture (racemic) of potent NSBBs and a weak alpha-1-receptor, was proposed. This new NSBB has been highlighted to be twice as potent as propranolol for beta-receptor blocking[22]. Several comparative trials comparing the outcomes of propranolol and carvedilol showed a > 20 percent decrease in the hepatic venous pressure gradient[23-25]. Rodrigues *et al*[26] outline the mechanisms of action for NSBB.

Challenges associated with NSBBs

NSBBs such as propranolol, nadolol, and carvedilol are pivotal in managing portal hypertension and preventing variceal bleeding in patients with cirrhosis. However, its use is associated with challenges and limitations that can affect patient outcomes and treatment adherence.

One of the primary challenges associated with the use of NSBBs is their cardiovascular side effects. NSBBs can cause significant bradycardia (slow heart rate) and hypotension (low blood pressure), which are particularly important in patients with advanced liver disease, who often have compromised cardiovascular systems[21,27]. These side effects can lead to poor medication tolerance and patients frequently report fatigue and dizziness, which can substantially affect their quality of life. This discomfort often results in poor adherence to the prescribed regimen, undermining the effectiveness of the treatment[27].

The use of NSBB medications has been known to exacerbate preexisting respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). The nonselective action of these beta-blockers on beta-receptors can lead to bronchoconstriction, further complicating the management of patients with concurrent respiratory disorders[28]. In certain circumstances, NSBBs can worsen circulatory dysfunction. For instance, in patients undergoing large-volume paracentesis to manage ascites, NSBBs may exacerbate paracentesis-induced circulatory dysfunction[21]. In addition, NSBBs can worsen the condition of patients with refractory ascites, making their use problematic in this subgroup of patients with advanced liver disease.

Furthermore, NSBBs are associated with an increased risk of HRS[29]. Some studies have suggested that these medications can increase the risk of HRS owing to their impact on renal blood flow and systemic vasoconstriction. This risk is particularly concerning given the already precarious renal function in many patients with decompensated cirrhosis [29]. Hepatic encephalopathy, a common complication of cirrhosis, is aggravated by NSBBs. These drugs can further reduce hepatic perfusion, potentially worsen liver function, and lead to increased encephalopathy. These side effects necessitate careful monitoring and therapeutic adjustments to balance the benefits and risks of NSBBs.

However, patient adherence to NSBB therapy remains a significant challenge[29]. The side effects and lifelong nature of the therapy can lead to poor adherence, which reduces the prophylactic effectiveness of the treatment and increases the risk of variceal rebleeding. Ensuring patient compliance with NSBB therapy requires extensive patient education and support, which can be resource-intensive.

Moreover, individual variability in the response to NSBBs further complicates their use. Not all patients achieve adequate reduction in portal pressure with NSBBs, necessitating additional therapies or alternative treatments such as TIPS[30]. This variability underscores the need for personalised treatment plans and regular monitoring to adjust therapy as needed. The effective use of NSBBs requires regular monitoring of heart rate and blood pressure to ensure appropriate dosing. This requirement can be challenging to meet in resource-limited settings, and adds to the overall burden of managing patients with cirrhosis. The need for frequent adjustments and close follow-up can strain healthcare resources and may not be feasible in all healthcare environments.

TIPS

Qi *et al*[31] attributed portal hypertension to the incidence of non-neoplastic portal vein thrombosis with an incidence rate of 10%-23%, leading to increased venous pressure and reduced blood flow to the liver[31,32]. Non-neoplastic portal vein thrombosis has also been associated with poor outcomes following liver transplantation, mortality, reduced blood flow, and contraindications to liver transplantation[33]. Moreover, Englesbe *et al*[34] and Sarin *et al*[35] reported a six-week mortality rate in almost 20% of patients with cirrhosis presenting with variceal bleeding, and its aetiology was attributed to increased portal vein pressure.

Currently, no consensus guidelines have elucidated the optimal prophylactic treatment for patients presenting with cirrhosis-induced variceal bleeding and portal vein thrombosis[36]. Current evidence suggests that this patient cohort has been associated with significant long-term complications and challenges in eradicating variceal bleeding in the long term [34]. However, several standard treatment interventions, including endoscopic band ligation and NSBBs, have been used to achieve immediate haemostasis and prevent re-bleeding[12]. Therefore, TIPS is recommended in patients who fail to respond to either of the two standard treatments[12].

Challenges associated with TIPS

One of the primary challenges of TIPS is the risk of hepatic encephalopathy[37,38]. This condition occurs in a significant proportion of patients following the procedure because of the shunting of blood away from the liver, which reduces the ability of the liver to detoxify harmful substances. This can lead to the build-up of toxins in the bloodstream, affecting brain function and resulting in symptoms ranging from mild confusion to severe cognitive impairment. Managing hepatic encephalopathy often requires additional medications and frequent monitoring, in addition to the complexity of post-TIPS care[38]. Shunt dysfunction is a major issue associated with TIPS complication. Over time, the shunt can become occluded or stenotic, leading to the loss of its therapeutic effect, necessitating regular surveillance with imaging studies such as doppler ultrasound to monitor shunt patency[39,40]. When dysfunction is detected, interventions such as angioplasty or shunt revision, which can be invasive and expensive, may be required. The need for ongoing surveillance and potential reinterventions places a significant burden on both patients and the healthcare system.

Procedure-related complications also pose a challenge for the use of TIPS. These complications include bleeding, infection, and injury to adjacent organs such as the bile ducts or hepatic arteries[41]. This procedure requires considerable expertise and is typically performed at specialist centres. The complexity of TIPS and the potential for severe complications highlight the importance of experienced interventional radiologists performing the procedure[41,42]. Another concern is the high cost of TIPS. The procedure requires follow-up care and potential re-interventions can be expensive, making TIPS less accessible in resource-limited settings and placing a financial strain on the patients and healthcare systems. The cost-effectiveness of TIPS is often weighed against its benefits, particularly in patients with advanced liver disease or those at high risk of complications[42].

Patient selection is crucial for the success of TIPS, but remains challenging. Identifying patients who will benefit the most from TIPS requires careful consideration of various factors, including liver function, portal hypertension severity, and other comorbidities[11]. Inappropriate patient selection can lead to suboptimal outcomes including higher rates of complications and mortality. Developing clear and evidence-based criteria for patient selection is essential to maximise the benefits of TIPS while minimising its risks[11]. Furthermore, the effect of TIPS on liver function is of significant concern. Although this procedure can effectively reduce portal hypertension, it can also compromise liver perfusion, potentially worsening liver function in some patients. This is particularly problematic in patients with a compromised liver function. A balance between reducing portal pressure and maintaining adequate liver function is difficult to achieve and requires careful management.

Finally, long-term data on the outcomes of patients who undergo TIPS are needed. While short-term benefits, such as reduced variceal bleeding and ascites control, are well-documented, the long-term impact on survival and quality of life is unclear. Ongoing research and long-term studies are needed to elucidate the full range of outcomes associated with TIPS and refine patient management strategies accordingly.

COMPARISON OF NSBBS AND TIPS

Evidence supporting TIPS for secondary prophylaxis

Historically, most evidence supporting TIPS for the secondary prevention of variceal bleeding comes from studies using bare metal stents, as illustrated in a meta-analysis by Miao *et al*[43]. One significant study compared endoscopic variceal ligation (EVL) with uncovered TIPS in 80 patients with cirrhosis who had variceal bleeding. The study found that TIPS significantly reduced the incidence of variceal rebleeding but did not improve the two-year survival rate[44]. Another trial compared drug therapies, including propranolol and isosorbide-5-mononitrate, with uncovered TIPS in patients with child-Pugh class B or C cirrhosis after the first episode of variceal bleeding. The trial revealed similar survival rates between the two groups. However, the TIPS group experienced more hepatic encephalopathy and required a higher number of re-interventions owing to in-stent thrombosis and other complications[11].

Transition to covered stents

Owing to the high incidence of in-stent thrombosis with bare-metal stents, there has been a shift toward the use of covered stents. Data on early treatment with covered TIPS *vs* endoscopic therapy combined with beta-blockers for acute variceal bleeding are limited, but promising. Two notable studies indicated a survival benefit in selected high-risk

populations, specifically in patients with child-Pugh class C or child-Pugh class B disease with active bleeding observed during diagnostic endoscopy[11]. However, these studies suggest that TIPS benefits may depend on early intervention and appropriate patient selection.

Recent uncontrolled studies and the need for further research

One uncontrolled study investigated the use of early TIPS for secondary prevention after controlling initial bleeding episodes. The study did not find a survival benefit of early TIPS compared to a historical cohort treated with EVL, highlighting the need for further research to refine patient selection criteria[45]. These findings underscore the importance of additional studies to determine the optimal criteria for selecting patients who would benefit most from TIPS for the secondary prevention of variceal bleeding[46].

Mechanism and indications

NSBBs and TIPS are used to manage portal hypertension and prevent variceal rebleeding. However, they have distinct mechanisms and indications. NSBBs, such as propranolol and nadolol, reduce portal pressure by decreasing cardiac output and inducing splanchnic vasoconstriction. They are primarily used to prevent initial and recurrent variceal bleeding[3]. Conversely, TIPS involves creating a channel within the liver to connect the portal vein to the hepatic vein, significantly reducing portal pressure and managing complications such as refractory ascites and hydrothorax.

Efficacy and survival

NSBBs effectively lower the risk of variceal bleeding; however, their effects on survival remain unclear. Clinical guidelines recommend these treatments in patients with high-risk varices[9]. TIPS has shown high efficacy in controlling variceal bleeding and improving survival, particularly in patients with refractory ascites or those at a high risk of rebleeding. However, TIPS is associated with a high risk of hepatic encephalopathy and requires careful patient selection [11].

Side-effects and complications

The side effects of NSBBs include bradycardia, hypotension, fatigue, asthma exacerbation, and COPD. They can also worsen paracentesis-induced circulatory dysfunction and refractory ascites, limiting their use in certain patients[16]. TIPS, although effective, is associated with risks such as hepatic encephalopathy, shunt dysfunction, and procedure-related complications. The high cost and need for specialised expertise further complicate its use. Table 1 shows a direct Comparison of NSBBs and TIPS.

FUTURE DIRECTIONS AND RECOMMENDATIONS IN THE COMPARISON BETWEEN TIPS AND NSBBS

The management of complications arising from portal hypertension in patients with cirrhosis often involves the use of NSBBs or TIPS. Both treatment modalities have demonstrated efficacy but have distinct advantages and limitations. Future research in this field should focus on refining the patient selection criteria, enhancing procedural techniques, and optimising combination therapies to improve patient outcomes.

Refining patient selection and early intervention

One of the most critical areas for future research is the development of more precise patient selection criteria. Current guidelines recommend TIPS for patients with refractory ascites or recurrent variceal bleeding. However, more nuanced stratification tools are required. Therefore, this study recommends conducting randomised controlled trials to evaluate the benefits of early TIPS initiation (within 72 hours of admission) in high-risk patients, particularly those with child-Pugh class B or C cirrhosis and active bleeding on endoscopy. These trials could help identify subgroups of patients who derive the most benefit from early intervention and bolster the findings detailed in the prospective studies by García-Pagán *et al*[45], Ruiz-Blard *et al*[46], Rudler *et al*[47], Lv *et al*[48,49], and García-Pagán *et al*[50]. Additionally, the development of biomarkers such as serum ammonia levels, inflammatory markers (*e.g.*, interleukin-6 and tumour necrosis factor-α), and genetic polymorphisms could improve risk stratification and help predict complications such as hepatic encephalopathy. By integrating these biomarkers with clinical parameters (*e.g.*, model for end-stage liver disease score and hepatic venous pressure gradient), more accurate risk stratification tools can be created to guide treatment decisions.

Optimizing combination therapies

Combining NSBBs with TIPS has shown promise in some studies, suggesting that a multifaceted approach may provide superior outcomes compared with either therapy alone[51,52]. Future clinical trials should explore the efficacy and safety of combination therapies in various patient populations, particularly those with refractory ascites or recurrent variceal bleeding. These trials should assess whether combining NSBBs with TIPS can reduce the risk of rebleeding and hepatic encephalopathy while improving survival. Furthermore, the potential synergistic effects of NSBBs with other vasoactive agents, such as alpha-1 blockers (*e.g.*, prazosin) or nitric oxide donors, should be investigated. Such combinations could offer a pharmacological alternative to invasive procedures such as TIPS, particularly in patients who are unsuitable candidates for the shunting procedure.

Table 1 Comparisons between nonselective beta-blockers and transjugular intrahepatic portosystemic shunt

Aspect	NSBBs	TIPS
Mechanism of action	Decreases cardiac output and induces splanchnic vasoconstriction to lower the portal pressure	Creates a channel between the portal and hepatic veins to reduce the portal pressure
Primary indications	Prevention of first and recurrent variceal bleeding	Management of portal hypertension complications such as variceal bleeding, refractory ascites, and hepatic hydrothorax
Efficacy	Effective in reducing variceal bleeding risk	Highly effective in controlling variceal bleeding and managing refractory ascites
Procedure	Non-invasive medications	Minimally invasive procedures performed by interventional radiologists
Side-effects	Bradycardia, hypotension, fatigue, exacerbation of asthma or COPD, paracentesis-induced circulatory dysfunction, and potential worsening of ascites	Risk factors of hepatic encephalopathy, shunt dysfunction, infection, and procedure-related complications
Survival impact	This can improve the survival of patients with high-risk varices	It can improve survival, particularly in patients with refractory ascites or those at a high risk of variceal rebleeding
Cost	Relatively low-cost as it involves medication	Expensive; Higher costs are attributed to the need for interventional procedures and possible subsequent shunt revisions
Follow-up and maintenance	Regular monitoring of heart rate, blood pressure, and dose adjustments may be necessary	Regular follow-up for shunt patency may require repeat imaging or interventions to maintain shunt function
Impact on hepatic encephalopathy	They can help reduce the incidence of hepatic encephalopathy when used appropriately	This involves a higher risk of postprocedural hepatic encephalopathy
Combination therapy	These are often combined with endoscopic treatment to achieve better outcomes	This may be combined with NSBBs to manage residual varices or incomplete portal decompression after the procedure
Clinical guidelines	American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend it for the prevention of variceal bleeding	The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend this for managing refractory complications of portal hypertension

NSBBs: Nonselective beta-blockers; TIPS: Transjugular intrahepatic portosystemic shunt; COPD: Chronic obstructive pulmonary disease.

Advancements in TIPS technology

Technological advancements in TIPS, particularly in the use of covered stents, have improved outcomes by reducing shunt dysfunction. Future research should focus on the development of next-generation stents, including drug-eluting stents, which may further reduce the risk of complications such as hepatic encephalopathy and shunt occlusion. In addition, minimally invasive techniques such as image-guided navigation systems can improve the precision of shunt placement and reduce procedure-related complications. Studies should also explore the long-term outcomes of these innovations, including their impact on shunt patency and the need for repeated interventions. By enhancing procedural techniques, we can minimise risks and improve the overall efficacy of TIPS.

Long-term outcome studies and patient-centred care

Although the short-term benefits of NSBBs and TIPS are well-documented, more comprehensive long-term studies are required to understand their impact on overall survival, quality of life, and healthcare costs. Large multicentre longitudinal cohort studies should follow patients for at least 5-10 years to provide robust data on the durability of these treatments. These studies should also incorporate patient-reported outcome measures to evaluate the impact of NSBBs and TIPS on patient quality of life, including symptoms such as fatigue, cognitive function, and physical activity levels. By focusing on patient-centred outcomes, we can better understand the real-world impacts of these therapies and tailor treatment plans according to individual needs.

Addressing hepatic encephalopathy

Hepatic encephalopathy remains a significant challenge after TIPS, and future research should investigate strategies to mitigate this risk. Adjunctive therapies, such as rifaximin, lactulose, or ammonia-lowering agents (*e.g.*, L-ornithine and L-aspartate), can be evaluated in RCTs to determine their efficacy in reducing the incidence of post-TIPS hepatic encephalopathy. Additionally, the role of gut microbiome modulation through probiotics or faecal microbiota transplantation should be explored as a potential strategy to reduce ammonia production and lower the risk of encephalopathy. Identifying patients at a higher risk of this complication pre-procedure using biomarkers or genetic profiling could also help tailor interventions more effectively.

Cost-effectiveness and resource allocation

The high cost of TIPS, including the procedure itself and the need for follow-up care, makes it imperative to conduct thorough cost-effectiveness analyses. Future research should compare the long-term costs and benefits of TIPS *vs* NSBBs, considering not only medical expenses but also indirect costs such as lost productivity and quality-adjusted life years.

These analyses will help health care providers and policymakers make informed decisions regarding resource allocation, particularly in resource-limited settings. Implementation studies should also evaluate the feasibility of integrating TIPS and NSBBs into routine clinical practice, identify barriers to their adoption, and propose strategies for improving access to these therapies.

Personalised medicinal approaches

The future management of portal hypertension in cirrhosis will be based on personalised medicine. Genetic profiling may play a key role in predicting individual responses to NSBBs and TIPS. For example, polymorphisms in beta-adrenergic receptors or genes involved in hepatic fibrosis can influence treatment outcomes and thus guide personalised therapeutic decisions. Machine learning models that integrate clinical, biochemical, and imaging data can help predict treatment responses and complications, enabling clinicians to tailor therapies according to individual patient profiles. By leveraging these advanced technologies, more precise and effective treatment strategies can be developed.

Enhancing patient education and support

Finally, improving patient education and support is crucial for optimising outcomes. Educational interventions, including digital health tools, such as mobile apps or telemedicine platforms, could enhance patient adherence to NSBB therapy and manage the expectations of those undergoing TIPS. Multidisciplinary care teams comprising hepatologists, interventional radiologists, nurses, and dietitians should be established to provide comprehensive care to patients with decompensated cirrhosis. Research should assess the impact of these teams on patient outcomes and satisfaction, ensuring that care is both effective and patient-centred.

The comparison between NSBBs and TIPS in the management of portal complications in patients with cirrhosis highlights the distinct benefits and challenges associated with each modality. NSBBs are a cornerstone in reducing portal pressure and preventing variceal bleeding but are often associated with significant cardiovascular and respiratory side effects, exacerbation of HRS, and hepatic encephalopathy. Variability in patient responses and the need for regular monitoring and dose adjustments further complicate their use. Despite their effectiveness, poor patient adherence due to the lifelong nature of the therapy and its side effects remains a significant hurdle. TIPS, while effective in reducing variceal rebleeding and managing refractory ascites, poses challenges, such as a high risk of hepatic encephalopathy, shunt dysfunction, and procedure-related complications. The high cost of the procedure and need for specialised expertise and follow-up care add to the complexity of its management. Patient selection is critical as inappropriate candidates may not benefit optimally and may experience higher complication rates.

CONCLUSION

Future research should focus on refining the patient selection criteria to identify which patients are most likely to benefit from each treatment modality. Advancements in TIPS technology such as the development of better stent materials and more precise imaging techniques are required to reduce complications and improve outcomes. Optimising combination therapies that leverage the strengths of both NSBBs and TIPS could provide superior outcomes compared to either treatment alone. Long-term studies are essential to understand the durability of TIPS and long-term adherence to NSBB therapy and to provide insights into overall survival, quality of life, and healthcare costs. Additionally, the development of personalised treatment plans based on patient characteristics, including genetic factors, disease severity, and comorbidities, could lead to more effective and safer outcomes. Cost-effectiveness analyses should compare the long-term costs and benefits of TIPS versus NSBBs, considering not only medical expenses, but also patient quality of life and productivity. Enhancing patient education and support to improve adherence to NSBB therapy and managing the expectations of those undergoing TIPS are crucial. By addressing these challenges and focusing on personalised and cost-effective care, healthcare providers can optimise the management of pulmonary hypertension complications in patients with cirrhosis. This will lead to improved patient outcomes, reduced complications, and a more efficient use of healthcare resources.

FOOTNOTES

Author contributions: Gadour E and Gardezi SA contributed equally; All authors read and approved the final manuscript.

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MINIREVIEWS

Advancement of indocyanine green fluorescence imaging technology in laparoscopic surgery for rectal cancer

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Abstract

Indocyanine green fluorescence imaging technology has been increasingly utilized in rectal surgery in recent years. As a safe tracer, indocyanine green can facilitate lymph node tracing, assess the blood supply at anastomotic sites, and localize tumour lesions during laparoscopic surgery, thereby resulting in favourable outcomes. This technology helps surgeons to achieve more precise diagnoses and treatments in laparoscopic procedures, thus ultimately benefiting patients. However, the current application of indocyanine green fluorescence imaging technology still lacks standardized regulations, and certain effects remain contentious. This study provides a comprehensive review of the application of indocyanine green in laparoscopic surgery for rectal cancer based on the pertinent literature.

Key Words: Indocyanine green fluorescence; Laparoscopic surgery; Rectal cancer; Lymph node; Blood supply

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Core Tip: Indocyanine green fluorescence imaging, which serves as a tracer for lymph node identification, blood supply assessment, and tumour localization, has been increasingly utilized in rectal surgery in recent years. This technique enhances surgical precision and improves patient outcomes. This study reviews the application of indocyanine green in laparoscopic rectal cancer surgery with references to the relevant literature.

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INTRODUCTION

Rectal cancer currently ranks as the third most globally prevalent malignant tumour, with an increasing incidence being observed[1]. The advent of minimally invasive surgical techniques has led to the widespread adoption of laparoscopic surgery for rectal cancer, and its therapeutic efficacy has been well established. In recent years, advancements such as total mesorectal excision have become standard surgical practices for middle- and low-position rectal cancers. Additionally, the introduction of neoadjuvant therapy has further alleviated surgical challenges and reduced postoperative recurrence rates. Nevertheless, issues such as incomplete lymph node dissection and postoperative anastomotic fistula continue to pose significant challenges for surgeons regarding traditional laparoscopic rectal cancer surgery. An increased focus on these concerns while improving both short-term and long-term outcomes for patients with rectal cancer remains a critical challenge in clinical practice. Indocyanine green (ICG) fluorescence is a clinically utilized near-infrared imaging agent that is known for its feasibility and safety profile. With ongoing advancements in medical technology, ICG has gradually been applied in tumour surgery and has yielded promising results that suggest favourable prospects for future use. In liver surgery, ICG can effectively delineate the anatomical structures of the liver, thereby facilitating precise hepatectomy. In gynaecological surgery, ICG serves as a valuable tool for assessing the metastasis of pelvic lymph nodes. Moreover, in urological surgery, ICG enables the accurate localization of kidney tumours and renal arteries. The application of ICG can effectively address the aforementioned challenges that are encountered during rectal cancer surgery. This article reviews the application of ICG fluorescence imaging technology in laparoscopic rectal cancer surgery by referencing recent research developments and relevant evidence-based medicine.

THE APPLICATION BASIS OF ICG FLUORESCENCE IMAGING TECHNOLOGY

Traditional dye tracers, such as methylene blue and nanocarbon, exhibit several disadvantages, including localized adhesion, suboptimal imaging quality, and the potential risk of peritoneal infection. ICG is an infrared contrast agent that is known for its excellent biocompatibility. When exposed to external light with wavelengths ranging from 750-800 nm, ICG emits longer wavelengths of near-infrared light. Due to its unique ability to emit light within the near-infrared spectrum, ICG is generally unaffected by self-luminescence, which may arise from haemoglobin and water in the blood components. By leveraging this characteristic, the ICG molecular fluorescence imaging system integrates fluorescence reception imaging with fluorescence excitation to facilitate the generation of ICG fluorescence images. This process employs a computer image processing system in combination with a high-sensitivity near-infrared fluorescence camera and a near-infrared excitation light source. Furthermore, the use of ICG enables real-time imaging during surgical procedures, thereby offering both simplicity and effectiveness.

Since the 1950s, ICG has been utilized in various applications, including the visualization of the retina and choroid, ophthalmic angiography, liver function assessments, and vascular system evaluations. With advancements in surgical techniques, ICG has been increasingly utilized for vascular imaging and functional assessments. Its applications have gradually expanded to include lymph node tracing, blood supply evaluation, and tumour localization, thereby demonstrating high feasibility and safety[2,3]. The costs of ICG reagents are relatively low, and they are also nonradioactive; thus, no additional protective measures are required during the procedures. Furthermore, ICG does not significantly stain human tissues under visible light conditions, which allows for unobstructed observation and operation during surgery.

Upon administration into the human body, ICG is metabolized by the liver and excreted in its intact molecular form *via* the bile ducts before being eliminated *via* faeces. Notably, it does not participate or travel in the enterohepatic circulation. Adverse reactions associated with ICG are infrequent; however, some patients may experience mild symptoms, such as facial flushing or sore throat. More serious reactions can include the development of hives, hypotension, dyspnoea, tachycardia, and anaphylactic shock. Due to its trace iodine content, ICG should be avoided in individuals with known iodine allergies. Since Nagata *et al*[4] first introduced the use of ICG in colorectal surgery in 2006, it has emerged as a promising tool for both the diagnosis and treatment of colorectal cancer. Furthermore, in recent years, ICG fluorescence imaging technology has been increasingly applied in the context of colorectal cancer surgery.

LYMPH NODE TRACING

Lymph node metastasis from rectal cancer is a primary contributor to recurrence and mortality in patients following surgical intervention. Consequently, comprehensive lymph node dissection within the regional area is crucial for achieving curative resection of rectal cancer. This scenario has significant implications for postoperative staging and the formulation of subsequent treatment strategies. However, there remains a challenge with respect to how to effectively and accurately perform lymph node dissection while enhancing both the positive lymph node detection rate and the total

number of dissected lymph nodes, which has consistently been a focal point in rectal cancer surgery.

Compared with traditional nanocarbon methods, ICG demonstrates superior accuracy in identifying sentinel lymph nodes and regional drainage lymph nodes during surgical procedures, as well as a greater capacity for detecting micrometastatic foci. The real-time *in vivo* imaging capabilities of ICG enable surgeons to accurately locate the regional drainage lymph nodes that are adjacent to tumours under physiological conditions, thereby facilitating effective lymphadenectomy with significant advantages. Typically, ICG lymph node tracing is preoperatively conducted *via* multiple injection points within the submucosal layer under colonoscopy or intraoperatively conducted around the tumour within the peritoneal cavity. The configuration method involves the dilution of ICG with sterilized water for injection, thus allowing for the preparation of ICG solutions at concentrations of 1.25, 2.5, or 5.0 g/L. Twelve to twenty-four hours prior to the operation, three to four injection sites are selected around the tumour under colonoscopic guidance, and 0.1-0.3 mL of the ICG solution is injected at each site. Additionally, the imaging duration can extend beyond 48 hours. The application method that is used during surgery remains consistent with this approach. Reports have indicated that the use of ICG for lymph node tracing yields a high detection rate during surgery, thereby suggesting its efficacy in guiding the extent of lymphadenectomy and increasing the retrieval of positive lymph nodes[5]. Chand *et al* [6] employed ICG for intraoperative lymph node tracing and observed visibility of nodes beyond the standard range of dissection; moreover, these nodes were subsequently confirmed to be metastatic after surgery, thereby reducing postoperative recurrence risks among patients. Watanabe *et al*[7] utilized ICG fluorescence imaging technology and revealed that the lymphatic flow from cancers located in the splenic area of the colon can directly reach regions surrounding the inferior mesenteric artery without traversing through either the left colonic artery or middle colonic artery. This finding challenges the traditional understanding of lymphatic flow pathways and underscores the application value of ICG in elucidating the lymphatic drainage patterns of patients with colorectal cancer.

The lymphatic drainage of lower to middle rectal cancer can occur simultaneously in the upwards, downwards, and lateral directions. The lateral transfer pathway follows the inner aspect of the distal iliac artery, whereby it reaches the lymph nodes surrounding the iliac vessels, which include the internal, obturator, external iliac, and common iliac nodes (Figure 1). According to previous research, the rate of lateral lymph node metastasis in patients with lower to middle rectal cancer may be as high as 26%[8]. Conventional total mesorectal excision typically involves lymph nodes that are located both above and below the iliac vessels but does not address the lateral lymph nodes that are situated outside of the rectal mesentery. Numerous retrospective studies have indicated that lateral lymph node metastasis is a significant risk factor for local recurrence in patients with rectal cancer who have undergone only total mesorectal excision[9]. In cases of pelvic recurrence of rectal cancer, up to 60% of patients may exhibit lateral-type recurrence[10]. Laparoscopic lateral lymph node dissection has emerged as an effective technique for clearing these nodes and can significantly reduce local recurrence rates following surgery while also improving patient outcomes[11].

A prospective randomized controlled trial (JCOG 0212) conducted by Japanese researchers demonstrated that the combination of total mesorectal excision with lateral lymph node dissection substantially decreases the likelihood of lateral local recurrence[12]. Therefore, for patients who are clinically suspected of or diagnosed with metastasis, the performance of concurrent lateral lymph node dissection is advisable. However, various challenges (such as the complex anatomy of the pelvic sidewall, the narrow interpelvic spaces, and oedema resulting from radiotherapy and chemotherapy) considerably complicate the laparoscopic identification and clearance of these laterally located lymph nodes. Therefore, the application of more precise lymph node localization methods to facilitate the clearance of pelvic lymph nodes that are adjacent to the rectum has emerged as a significant challenge that requires resolution. To address this issue, recent advancements in tracer imaging technology have gradually demonstrated the potential value of this technology in clinical applications.

However, lateral lymph node dissection may result in damage to the blood vessels and nerves along the pelvic lateral wall, which increases the incidence of postoperative urinary dysfunction and subsequently diminishes patients' quality of life. The application of ICG fluorescence imaging technology during lymph node dissection aids in accurately locating target lymph nodes while minimizing unnecessary injury to the surrounding blood vessels and nerves. According to reports, the utilization of ICG can identify lateral lymph nodes in 92% of patients, thereby facilitating lateral lymph node dissection[5]. Moreover, research findings have indicated that, compared with standard total mesorectal excision, nerve-sparing lateral lymph node dissection is associated with a greater prevalence of sexual and urinary function disorders. The preservation of the pelvic plexus nerve during lateral lymph node dissection protects neural structures; additionally, it does not compromise survival benefits, thus enabling most patients to maintain satisfactory urinary function[13] (Table 1).

EVALUATION OF THE BLOOD SUPPLY TO THE ANASTOMOSIS

Anastomotic fistula is a significant complication following rectal cancer surgery, and it can lead to prolonged hospital stays, increased health care costs, elevated mortality rates, and adverse effects on both short-term and long-term patient prognosis. Despite advancements in neoadjuvant therapy, the implementation of total mesorectal excision, improvements in laparoscopic surgical instruments, and improvements in surgical techniques have markedly improved postoperative outcomes for patients with colorectal cancer; however, the incidence of anastomotic leakage has not exhibited a corresponding decline. The occurrence of anastomotic fistula is due to the interplay of multiple factors, with blood supply to the anastomosis being one of the most critical determinants. The vascular supply to the left hemicolon is particularly intricate, as it involves several arteries, including the inferior mesenteric artery, left colonic artery, and middle colonic artery, as well as the marginal artery of Drummond and the arc of Riolan (Figure 2). Variations in or the absence of these vessels

Table 1 Lymph node tracing

Ref.	Journal	Year	Application
Nagata *et al*[4]	*Anticancer Res*	2006	Colorectal cancer
Dai *et al*[5]	*Front Med (Lausanne)*	2022	Lateral pelvic lymph node of rectal cancer
Chand *et al*[6]	*Tech Coloproctol*	2018	Colon cancer
Watanabe *et al*[7]	*Int J Colorectal Dis*	2017	Splenic flexural colon cancer
Kanemitsu *et al*[13]	*Clin Colon Rectal Surg*	2020	Lateral pelvic lymph node of rectal cancer

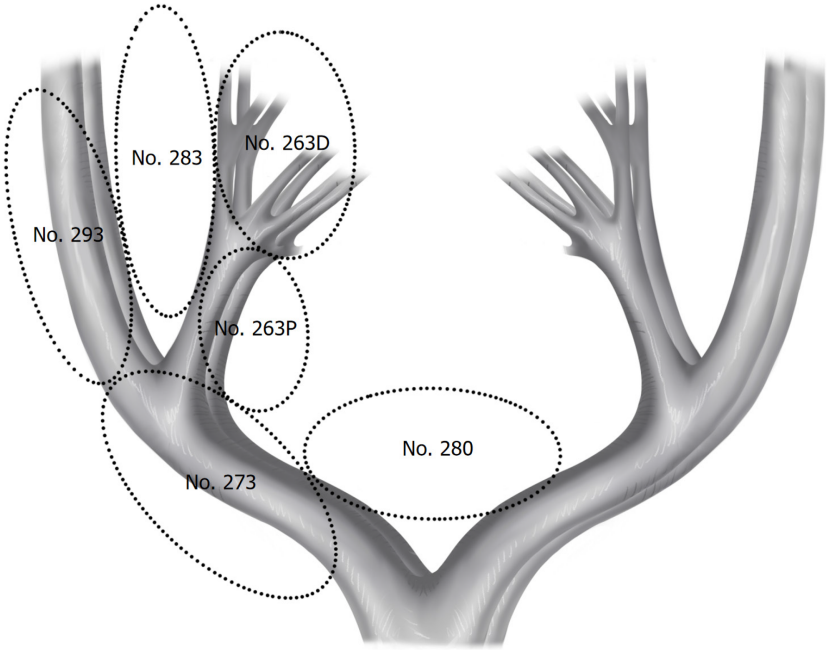


Figure 1 The vascular supply to the colon.

can lead to inadequate blood supply to this region. Patients with a history of ischaemic bowel disease or those who have undergone neoadjuvant chemoradiotherapy are at heightened risks for such complications. Compared with postoperative prevention and treatment strategies, the real-time evaluation of blood supply perfusion at the anastomosis site during surgery offers a more precise approach for mitigating the development of postoperative anastomotic fistula. Currently, the clinical assessment of blood supply during surgery primarily relies on surgeon experience; moreover, surgeons evaluate various factors, such as changes in intestinal wall colour before and after anastomosis, bleeding intensity at the intestinal junctions, and capillary filling. However, this method lacks accuracy. During open surgery, the surgeon is able to assess the blood supply of the intestine by examining the vascularity of the mesenteric fat pad and palpating the pulsation of the mesenteric vessels. However, this assessment is not feasible during laparoscopic surgery. Although laser Doppler flowmetry, Doppler colour ultrasound, and oxygen molecular light instruments can be employed to evaluate blood supply during surgical procedures, their clinical application remains limited because of issues related to convenience and a lack of rigorous validation.

ICG fluorescence imaging technology is a straightforward and effective method for evaluating tissue blood flow perfusion during laparoscopic surgery, and it demonstrates high safety and feasibility, as well as promising application prospects. The configuration method involves the dilution of 25 mg of ICG in 10 mL of sterilized water for injection to produce a solution with a concentration of 2.5 g/L ICG. Additionally, the recommended dosage ranges from 0.1-0.3 mg/kg and is administered *via* intravenous injection. In cases of repeated administrations, the maximum daily dosage should not exceed 5 mg/kg. Following the separation of the proximal intestinal mesentery during laparoscopic procedures, a preexcision line is established, after which ICG is intravenously administered to assess the blood supply at this line. In cases where the blood supply appears to be inadequate, the preexcision line can be repositioned to an area with improved vascularity closer to the distal end. Once anastomosis has been completed, ICG is injected again to evaluate the blood supply at the anastomotic site; if insufficient perfusion is detected, resection of the anastomosis may be necessary, followed by reanastomosis.

In 2010, Kudszus *et al*[14] pioneered the application of ICG fluorescence imaging technology for assessing the anastomotic blood supply in colorectal cancer surgeries, thereby resulting in a 4% reduction in the incidence of postoperative anastomotic fistulas. The PILLAR II clinical study utilized a fluorescence imaging system to evaluate the anastomotic blood supply in 139 patients who underwent colorectal resection and subsequent reanastomosis due to poor

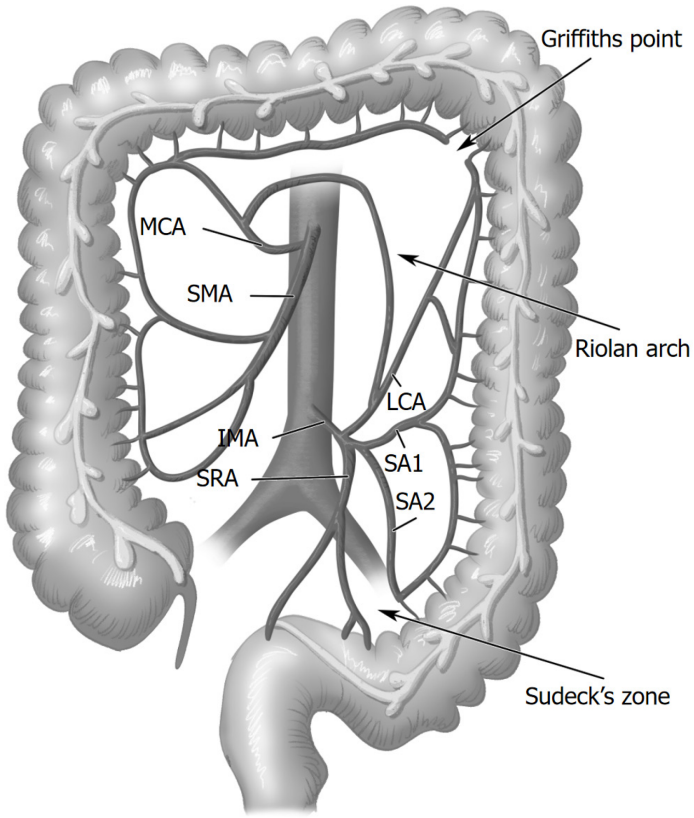


Figure 2 Lateral lymph nodes surrounding the rectum. MCA: Middle colic artery; SMA: Superior mesenteric artery; IMA: Inferior mesenteric artery; SRA: Superior rectal artery; LCA: Left colic artery; SA: Sigmoid artery.

perfusion. Remarkably, no instances of postoperative anastomotic fistulas occurred among these patients; thus, this observation underscores the notion that ICG fluorescence imaging can promptly and effectively identify and address issues related to the anastomotic blood supply, thereby reducing the rates of postoperative complications[15].

A multicentre retrospective study conducted in Japan in 2020 included 422 rectal cancer patients who underwent surgical interventions *via* ICG fluorescence imaging technology. This investigation revealed that surgical decisions were altered for 5.7% of the patients based on findings from ICG fluorescence imaging assessments, thus consequently leading to a nearly 6% decrease in the incidence of postoperative anastomotic fistulas while also minimizing secondary surgeries and shortening hospital stays[2]. Chan *et al*[16] conducted a meta-analysis demonstrating that the use of ICG to assess blood supply before and after intestinal resection during surgery can significantly reduce the incidence of postoperative anastomotic fistulas. Moreover, Alexander *et al*[17] reported a case of acute ischaemic bowel disease that improved following treatment with laparoscopic ICG fluorescence imaging technology. This scenario represents a rare instance of ICG fluorescence imaging being utilized in the context of ischaemic bowel disease, thereby highlighting its advantages in evaluating local blood supply conditions and enhancing treatment outcomes.

Some researchers have employed spectral analysis software to quantitatively analyse the fluorescence duration and intensity at the anastomotic site, with an aim of obtaining more accurate assessments of blood supply; however, additional clinical data are needed to further substantiate these findings[18]. In low rectal surgeries, wherein the operative space is limited and anastomosis poses challenges, the application of ICG fluorescence imaging technology has been demonstrated to decrease the occurrence of postoperative anastomotic complications[19]. Scholars have integrated robotic surgery with ICG fluorescence imaging technology in cases involving low rectal cancer. This approach not only capitalizes on the superior field visibility and enhanced operability provided by robotic systems but also facilitates improved identification of anatomical layers and evaluation of anastomoses during procedures, thereby increasing surgical safety[20].

When the position of the partial anastomosis is lower and the bowel is thickened or difficult to visualize at the posterior wall of the anastomosis, the use of a laparoscopic fluorescence imaging system for observation may demonstrate challenges. This can subsequently lead to insufficient judgement during surgery. Some scholars have suggested that the utilization of a fluorescent rectal endoscope *via* the anus may yield more accurate results[21]. However, recent findings from the PILLAR III study indicate that although ICG fluorescence imaging technology can effectively assess the blood supply to the anastomosis in patients, it does not significantly reduce the incidence of anastomotic fistulas[22]. Additionally, a multicentre randomized controlled trial conducted in Italy demonstrated that although ICG fluorescence imaging technology was intraoperatively used to evaluate blood supply and implement timely interventions in participants in the experimental group, there was no significant difference observed in fistula occurrence between this group and the control group[23]. Consequently, further large-sample, multicentre studies are warranted to provide additional evidence-based support regarding the application of ICG for intraoperative assessments

of the anastomotic blood supply (Table 2).

LOCALIZATION OF DISTANT METASTASES

The liver serves as the primary target organ for haematogenous metastasis in patients with colorectal cancer. Although the surgical resection of liver metastases is an effective treatment approach, some patients continue to experience recurrence after surgery. This may be attributed to the challenges associated with the preoperative detection of microscopic metastases *via* imaging modalities and the difficulty in intraoperatively identifying these metastases. ICG has emerged as a valuable tool for visualizing liver metastases and was utilized even prior to its application in colon and rectal cancers. For the localization of liver metastases originating from colorectal cancer, an intravenous injection of 0.5 mg/kg of a 2.5 g/L ICG solution can be administered 24 hours prior to the surgical procedure. Ishizawa *et al*[24] were among the first researchers to report the use of ICG for visualizing liver metastases in 12 cases of colorectal cancer with hepatic involvement; notably, 6 cases exhibited clear visualization of liver metastases, thus demonstrating high sensitivity. Additionally, researchers conducted a retrospective analysis involving clinical data from 15 patients diagnosed with colorectal cancer liver metastasis and reported that the use of ICG during surgery significantly increased the detection rate of these lesions[25]. According to the literature, ICG fluorescence imaging can identify liver metastases with a minimum diameter of 1 mm during surgical procedures; however, due to the limited penetration depth of this imaging technology, it is recommended that deep-seated lesions be assessed in conjunction with intraoperative ultrasound techniques[26]. Therefore, ICG can be utilized during laparoscopic colorectal cancer surgery to identify liver metastases, thus facilitating timely intraoperative management or subsequent postoperative treatment.

Similar to liver metastases, small peritoneal metastatic lesions are challenging to detect and can easily result in recurrence following surgery in patients with rectal cancer. Barabino *et al*[27] employed ICG to visualize peritoneal metastatic lesions in ten patients with colorectal cancer metastasizing to the peritoneum, whereby they achieved a visualization rate of 72.4% for lesions confirmed by pathology as being metastatic cancer. Therefore, the use of ICG for real-time imaging during surgical procedures has the potential to identify peritoneal micrometastatic lesions that are often difficult to discern either preoperatively or intraoperatively, thus allowing for the removal of these lesions and thereby increasing the survival rates of rectal cancer patients. However, relatively few studies have investigated the application of ICG in cases of peritoneal metastasis. In addition, a single-centre study indicated that quantitative ICG seems to be useful for the assessment of nonmucinous colorectal peritoneal metastases[28] (Table 3).

LIMITATIONS AND APPLICATION PROSPECTS

Despite the increasing application of ICG fluorescence imaging technology in surgical procedures, several factors can influence surgeons' judgements during operations. These factors include the amount of injected ICG, observation time, injection site, injection method, fluorescence intensity, external lighting conditions, distance between the laparoscopic lens and the tissue or organ, and individual patient differences. Insufficient fluorescence intensity of ICG may impair the surgeon's evaluation of the blood supply to anastomoses, thus potentially leading to postoperative complications such as anastomotic fistulas. Indeed, the fluorescence intensity is correlated with the administered dosage; however, a standardized injection protocol and optimal concentration for ICG have yet to be established. Reports have indicated that even when ICG fluorescence imaging is employed to intraoperatively assess blood supply, some patients still experience postoperative anastomotic fistulas due to nonstandardized injection techniques and observation times[29].

According to previous studies, the imaging times following ICG injections can vary across different vascular systems (ranging from several seconds to a few minutes). Consequently, if the optimal imaging time cannot be established, it may adversely affect the assessment of blood supply at the anastomotic site. Importantly, for patients undergoing neoadjuvant chemoradiotherapy, potential damage to lymphatic vessels caused by preoperative treatment may hinder the visibility of the lymph nodes that are detectable with ICG during surgery, thereby impacting the effectiveness of ICG imaging. Ankersmit *et al*[30] conducted a meta-analysis that demonstrated insufficient diffusion of fluorescence dye around tumours in colorectal surgeries, which led to suboptimal localization of lymph nodes and tumour visualization. In clinical practice, advanced-stage tumours may exhibit challenges such as thrombosis in lymphatic vessels due to cancer emboli. This scenario can result in the partial enlargement of lymph nodes that are not visible or lead to the partial invasion of tumours into the intestinal wall, which obstructs lymphatic drainage and manifests as false-positive results. Therefore, targeted lymphadenectomy remains necessary during surgery based on individual circumstances.

Moreover, individual differences among patients may significantly influence the metabolism and excretion of ICG, thereby affecting its imaging efficacy. For example, the half-life of ICG is extended in elderly patients and in those patients with renal insufficiency, whereas it is reduced in younger patients and in individuals with liver dysfunction. To effectively address these individual variations in clinical practice, several measures can be implemented. First, individualized ICG dosing regimens can be developed based on factors such as patient age, sex, health status, and liver function. By adjusting both the dosage and timing of injections, the metabolism and excretion of ICG within the patient's body can be optimized to enhance imaging outcomes. Second, the improvement of the detection sensitivity of imaging devices to accommodate low-dose ICG applications is essential. This enhancement can help to mitigate instances of suboptimal imaging results caused by attenuation effects from ICG within the body. Third, prior to conducting ICG imaging procedures, a thorough evaluation of liver and kidney function indicators should be performed to determine appropriate dosages and injection intervals for each patient. By implementing these strategies, individual differences can be

Table 2 Evaluation of blood supply to anastomosis

Ref.	Journal	Year	Application
Kudszus *et al*[14]	*Langenbecks Arch Surg*	2010	Colorectal cancer
Jafari *et al*[15]	*J Am Coll Surg*	2015	Left colon and rectal cancer
Watanabe *et al*[2]	*Surg Endosc*	2020	Rectal cancer
Chan *et al*[16]	*Surgery*	2020	Colorectal cancer
Alexander *et al*[17]	*Int J Surg Case Rep*	2019	Acute mesenteric ischemia
Son *et al*[18]	*Surg Endosc*	2019	Colorectal cancer
Wada *et al*[19]	*Int J Clin Oncol*	2019	Rectal cancer
Skrovina *et al*[20]	*Wideochir Inne Tech Maloinwazyjne*	2020	Rectal cancer
Liang *et al*[21]	*Zhonghua Wei Chang Wai Ke Za Zhi*	2020	Rectal cancer
Jafari *et al*[22]	*Dis Colon Rectum*	2021	Left colon and rectal cancer
De Nardi *et al*[23]	*Surg Endosc*	2019	Colorectal cancer

Table 3 Localization of extraperitoneal metastases from rectal cancer

Ref.	Journal	Year	Application
Ishizawa *et al*[24]	*Cancer*	2009	Liver metastasis
Patel *et al*[25]	*J Gastrointest Cancer*	2023	Liver metastasis
Piccolo *et al*[26]	*J Laparoendosc Adv Surg Tech A*	2021	Liver metastasis
Barabino *et al*[27]	*Eur J Surg Oncol*	2016	Peritoneal metastasis
González-Abós *et al*[28]	*Dis Colon Rectum*	2022	Peritoneal metastasis

effectively managed, thereby ultimately improving both the accuracy and safety associated with ICG imaging.

The application of ICG in laparoscopic surgery is progressively advancing. When ICG is combined with emerging technologies, its potential applications may be further expanded. In laparoscopic procedures, the integration of intraoperative navigation technology enables surgeons to obtain real-time fluorescence images of the surgical field during operations, thereby facilitating more precise localization of diseased tissues and allowing for the formulation of more rational surgical strategies. Ryu *et al*[31] employed intraoperative fluorescence navigation technology in laparoscopic left-sided colon and rectal cancer surgery. Additionally, they conducted evaluations of blood flow, fluorescence clip marking procedures, ureteral navigation procedures and fluorescence vessel navigation procedures to identify and evaluate both lesions and the surrounding tissue structures. The findings demonstrated significant efficacy and contributed to a reduction in the incidence of postoperative complications. Moreover, the incorporation of machine learning and artificial intelligence significantly enhances the utility of ICG in laparoscopic surgery. By training machine learning models, clinicians can leverage feature information from ICG fluorescence imaging to automatically identify and analyse pathological tissues. This approach not only improves diagnostic accuracy but also provides avenues for personalized treatment options. In laparoscopic rectal cancer surgeries, the use of ICG fluorescence imaging in conjunction with machine learning techniques allows surgeons to determine resection margins with greater precision, thereby ensuring both thoroughness and safety during the procedures[32]. Concurrently, artificial intelligence can assist physicians by monitoring changes in ICG fluorescence imaging in real time throughout the operation, thus enabling prompt detection and management of any abnormalities that may arise. This ability for real-time monitoring not only enhances surgical safety but also provides valuable decision support during operations. The integration of ICG with intraoperative navigation systems, as well as machine learning and artificial intelligence technologies, demonstrates significant potential to improve both the accuracy and safety of surgical interventions while also offering possibilities for tailored treatments. As these technologies continue to advance and develop, the application of ICG in laparoscopic rectal surgery is expected to become increasingly comprehensive and sophisticated.

CONCLUSION

In conclusion, ICG fluorescence imaging technology has proven to be a valuable tool for lymph node tracing, assessment of the blood supply at anastomotic sites, and localization of distant metastatic lesions during laparoscopic rectal cancer surgery. However, the operating procedures for ICG fluorescence imaging remain to be clearly defined, and certain

effects require further validation. Therefore, it is essential to conduct more prospective multicentre studies and establish standardized operating guidelines to facilitate the broader adoption of ICG in the future.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Logistic regression analysis of pathological features of bone metastasis in colorectal cancer and related influencing factors after surgery

Qiu-Yan Tang, Wei Yu

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a common malignant tumor in the digestive system, whose main treatment comprises surgical resection, radiotherapy and chemotherapy, and targeted drug therapy. At present, the radical resection of CRC is the main way of achieving an early cure.

AIM

To investigate the logistic regression analysis of bone metastasis after CRC surgery and related influencing factors.

METHODS

We selected 100 patients who underwent surgery for CRC and were admitted from February 2018 to February 2024, collected the general data of bone metastasis, and collected the pathological characteristics of patients with bone metastasis. Next, we divided them into groups with and without bone metastasis (Bone metastases group, n = 44; no bone metastases group, n = 56), compared the clinical data of the two groups, and analyzed the risk factors of bone metastasis using logistic regression analysis.

RESULTS

Among the 100 patients, the mean age was 54.33 ± 8.45 years, and most were male (54.55%). The proportion of patients with lytic bone changes was 43.18%. The most common location of combined bone metastasis was the pelvis, whereas only 5 patients had limb transfer. There was a higher incidence of lung than of pancreatic or liver metastases. Regression analysis showed that the primary

location of the cancer was rectal cancer. Lymph node involvement, lung metastasis, and no postoperative chemotherapy were the risk factors for postoperative bone metastasis in patients who underwent surgery for CRC ($P < 0.05$).

CONCLUSION

Rectal cancer, lymph node involvement, complicated pulmonary metastasis, and no postoperative chemotherapy treatment can help predict high risk of bone metastasis in CRC.

Key Words: Colorectal cancer; Bone metastasis; Pathological characteristics; Influencing factors; Clinic treatment

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Core Tip: Early identification of bone metastasis risk in colorectal cancer patients is critical, especially pre- and post-surgery. Targeted interventions for risk factors are essential. These may include bone-protecting drugs, dietary improvements, and exercise to boost bone health. Regular monitoring through imaging and tests helps detect early signs of bone metastasis, allowing for timely treatment and improved patient outcomes.

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INTRODUCTION

Colorectal cancer (CRC) is a prevalent malignancy in the digestive system, with a significant effect on global health. Recent epidemiological data indicate a rising trend in the incidence of bone metastasis among patients with CRC, which poses a substantial challenge to clinical management. Bone metastasis, occurring in a considerable subset of CRC cases, is associated with increased morbidity and reduced survival rates. Current research efforts are focused on identifying risk factors, understanding the molecular mechanisms, and developing targeted therapies to mitigate the effect of bone metastasis. Despite advancements, several challenges remain unresolved. These include the lack of early detection markers, the complexity of metastatic pathways, and the heterogeneity of patient responses to treatment. Furthermore, the limited understanding of the interaction between tumor cells and the bone microenvironment hinders the development of effective preventive and therapeutic strategies. Addressing these issues is crucial for improving patient outcomes and reducing the burden of CRC-associated bone metastasis.

At present, radical resection of CRC is the main way to cure it at an early stage[1]. However, some patients experienced cancer lesion recurrence, distant metastasis and postoperative metastasis of the lymph node, leading to surgical failure. The lung, liver, and pancreas are the main sites of cancer cell metastasis after CRC, whereas the incidence of bone metastasis is relatively rare[2,3]. However, with the continual aging of the population and the formation of bad national living habits, the risk of bone metastasis in patients with CRC after surgery has increased. If the risk factor of bone metastasis after CRC surgery can be identified, targeted intervention measures could be given earlier, which would help ensure the efficacy of surgery and postoperative recovery of patients. However, in previous studies, the description of the pathological characteristics of bone metastasis after CRC and the analysis of the risk factors leading to the occurrence of bone metastasis are rare. In view of this, the present study retrospectively analyzed the medical records of 100 patients undergoing CRC surgery in our hospital, summarized the pathological characteristics of bone metastasis in patients after CRC, and analyzed the risk factors.

MATERIALS AND METHODS

General information

This was a retrospective analysis of 100 patients with CRC admitted to the hospital from February 2018 to February 2024, including 64 men and 36 women, aged 34 to 68 years (mean age: 51.00 ± 11.25). All patients met the diagnostic criteria specified in the Spanish Society of Medical Oncology clinical guidelines for diagnosis and treatment of metastatic CRC (2018)[4]. Inclusion criteria were: (1) Patients could tolerate surgical treatment of rectal cancer; (2) Patients had not developed extensive tumor metastasis; and (3) Informed consent from patients and family members was obtained. Exclusion criteria were patients who had these characteristic: (1) Severe underlying disease and poor cardiopulmonary function; (2) Severe coagulation dysfunction that could not be corrected; (3) Tumors that had invaded the large vessels; (4) Large tumor volume and serious adhesion to surrounding tissues; (5) Mental diseases; (6) Estimated survival of < 3 months; or (7) Severe infection (Figure 1).

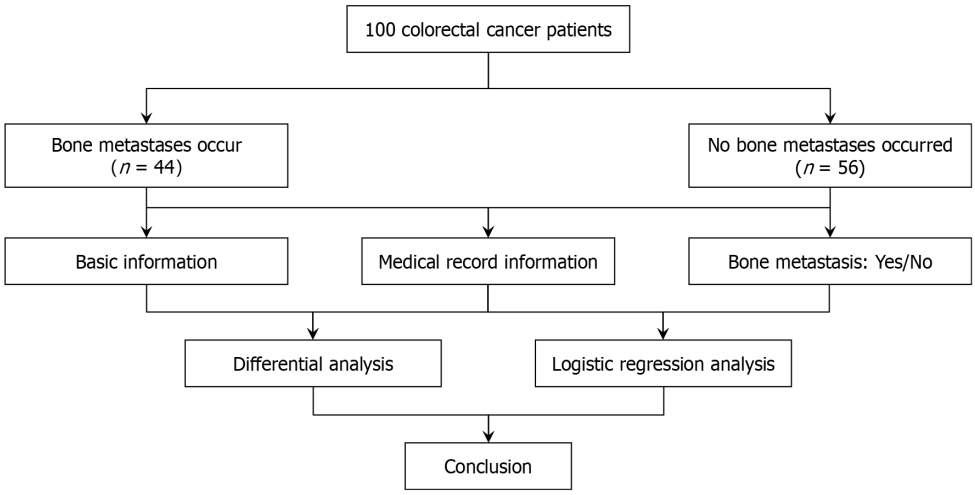


Figure 1 Flowchart of the study.

Data collection

We selected 100 patients who underwent surgery for CRC and were admitted from February 2018 to February 2024. The data collection process involved a systematic review of medical records, with specific attention to the following steps and methods: (1) Selection of medical records: Medical records were selected based on the diagnosis of CRC and the treatment period specified (February 2023 to April 2024); (2) Initial screening: Records were initially screened to ensure they met the inclusion criteria, which included a confirmed diagnosis of CRC and completion of treatment within the specified time frame; and (3) Detailed review: Each selected record was reviewed in detail to extract relevant information. This process was conducted by trained medical personnel who were familiar with the specific data points required for the study.

Quality control

The survey has strict quality control, and the investigators involved in the survey had received professional training. After pre-experiment, the internal consistency reliability Cronbach's α coefficient of the general data of the survey was 0.83, and of each dimension was 0.62-0.84. The retest reliability was 0.82, 0.70-0.85, and the content validity was 0.93.

Observational indicators

The observational indicators include: (1) Analysis of postoperative bone metastasis in patients undergoing CRC surgery; (2) Univariate analysis of affected postoperative bone metastases in patients undergoing CRC surgery. According to whether the patients developed bone metastasis, the 100 patients with CRC were divided into bone metastasis (n = 44) and no bone metastasis (n = 56) groups, and the medical records of the two groups were compared; and (3) Multivariate analysis of affected postoperative bone metastases in patients undergoing CRC surgery.

Statistical analysis

All the data of this study were entered into SPSS 25.0 for analysis, including the expression form n (%). The χ^2-test was used to measure whether data conformed to a normal distribution, and the expression form was mean ± SD. We also used a t-test and risk factor analysis using the logistic multiple regression model. $P < 0.05$ represents a statistically significant difference.

RESULTS

Among the 100 patients with CRC who underwent surgical treatment, the incidence of bone metastasis was 44.0% (44/100). These patients' age ranged from 45 to 63 years (mean age 54.33 ± 8.45). The clinical data of the two groups are shown in Table 1. In terms of the factors affecting the postoperative development of bone metastases, significant differences were observed in tumor primary location, postoperative chemotherapy, combined pulmonary metastasis, and lymph node involvement ($P < 0.05$) (Table 2). For items that showed differences in the univariate tables, the multiple logistic regression model showed that the primary location of tumor was the rectum. Complicated lymph node involvement, complicated lung metastasis, and no postoperative chemotherapy were other risk factors affecting postoperative bone metastasis ($P < 0.05$) (Tables 3 and 4).

Table 1 Pathological characteristics of postoperative bone metastases in patients undergoing colorectal cancer surgery

Items		Cases (n = 44)	Proportion, %
Age, years	54.33 ± 8.45		
Sex	Male	24	54.55
	Female	20	45.45
The primary location of the tumor	Colon	11	25.00
	Rectum	33	75.00
Tumor diameter, cm	4.02 ± 1.02		
Osteopathic changes	Osteolytic	19	43.18
	Osteogenic	14	31.82
	Mixed bone destruction	11	25.00
Type of bone metastasis	Single type	15	34.09
	Multiple type	29	65.91
Infiltration depth	T1-T2	14	31.82
	T3-T4	30	68.18
Lymphatic metastasis	Yes	29	65.91
	No	15	34.09
Location of bone metastases	Skull	8	18.18
	Pelvis	18	40.91
	Trunk	6	13.64
	Four limbs	5	11.36
	Spinal column	7	15.91
Bone metastasis organs	Liver	11	25.00
	Lung	26	59.09
	Pancreas	7	15.91

DISCUSSION

Bone metastasis, as a malignant tumor originating outside the bone tissue, is transferred to bone tissue, causing bone injury and pain[5]. At present, the clinically accepted mechanisms of bone metastasis include: (1) Primary tumor cells infiltrate the vasculature; (2) Tumor cells are released into the blood circulation; (3) Tumor cells stay in the vascular wall in the bone marrow; (4) Tumor cells overflow through endothelial cells and proliferate outside the vessels; and (5) Blood transport is established in the metastatic tumor cells, forming bone metastasis[6]. After bone metastasis, owing to symptoms such as pathological fracture and pain, patients experience adverse events such as limited limitation and decreased quality of life, which have a negative effect on the efficacy of surgery and their prognosis for recovery[7].

In this study, by compiling the pathological data of patients with bone metastasis following CRC in our hospital, we found that male patients with invasion of T 3 to T 4 were more likely to develop bone metastases[8,9]; the patients with bone metastases had osteolytic change and primary tumor of rectal cancer, 43.18% and 75.00%, respectively; and the incidence of patients with multiple bone metastases was higher than that of solitary bone metastases[10,11]. Through logistic regression analysis, we found that the primary location of tumor was rectal cancer, lung metastasis, no postoperative chemotherapy, and lymph node involvement were risk factors for bone metastasis in patients undergoing CRC surgery ($P < 0.05$).

To take these risk factors in turn: (1) The primary tumor site was rectal cancer. Because of the complex lymphatic reflux route of the rectum, the lower vein returns to the inferior vena cava, without a valve, leading to the characteristics of slow blood velocity. When tumor cells detach, they easily adhere to the location and form metastases[12-15]. The rectal lymphatic drainage for the inferior mesenteric artery lymph nodes is situated not only in the mesentery, but also laterally and below. When the drainage way is more complex, surgery is more difficult; thus, the postoperative risk for bone metastases of patients with rectal cancer is higher than that of those with colon cancer; (2) No postoperative chemotherapy: Postoperative adjuvant chemotherapy measures can eliminate the remaining lesions in the operation, and reduce the probability of recurrence and metastasis of cancer lesions in patients with CRC after surgery; (3) Lymph node involvement: Lymph nodes are one of the immune organs of the human body and can remove toxic and harmful substances. When tumor cells invade the body, the patient's immune system is damaged, increasing the risk of immune

Table 2 Single variables affecting the occurrence of postoperative bone metastases in patients undergoing colorectal cancer surgery, *n* (%)

Variables		Bone metastases (*n* = 44)	No bone metastases (*n* = 56)	t/χ^2	*P* value
Age	≤ 60	24 (54.55)	36 (64.29)	0.974	0.324
	> 60	20 (45.45)	20 (42.86)		
Sex	Male	24 (54.55)	40 (71.43)	3.048	0.081
	Female	20 (45.45)	16 (28.57)		
The primary location of the tumor	Colon	11 (25.00)	30 (53.57)	8.315	0.004
	Rectum	33 (75.00)	26 (46.43)		
Tumor diameter	< 5 cm	31 (70.45)	34 (60.71)	1.028	0.311
	≥ 5 cm	13 (29.55)	22 (39.29)		
Osteopathic changes	Osteolytic	19 (43.18)	15 (26.79)	2.985	0.225
	Osteogenic	14 (31.82)	22 (39.29)		
	Mixed bone destruction	11 (25.00)	19 (33.93)		
Infiltration depth	T1-T2	14 (31.82)	27 (48.21)	2.738	0.098
	T3-T4	30 (68.18)	29 (51.79)		
Postoperative chemotherapy	Yes	11 (25.00)	45 (80.36)	30.644	< 0.001
	No	33 (75.00)	11 (19.64)		
Combined lung metastases	Yes	26 (59.09)	18 (32.14)	7.262	0.007
	No	18 (40.91)	38 (67.86)		
Concomitant liver metastasis	Yes	11 (25.00)	24 (42.86)	3.454	0.063
	No	33 (75.00)	32 (57.14)		
Concomitant pancreatic metastasis	Yes	7 (15.91)	11 (19.64)	0.233	0.630
	No	37 (84.09)	45 (80.36)		
Lymph node involvement	Yes	29 (65.91)	19 (33.93)	10.096	0.002
	No	15 (34.09)	37 (66.07)		

Table 3 Variable assignments

Independent variable	Assignment
The primary location of the tumor	"rectum" = 1, "colon" = 0
Lymph node involvement	"yes" = 1, "no" = 0
Pulmonary metastasis	"yes" = 1, "no" = 0
Postoperative chemotherapy	"yes" = 1, "no" = 0

disorders, induced lymphocyte dysplasia, and tumor metastasis; and (4) Lung metastasis: Because of the specific anatomy of the lung, when tumor cells invade the lung, they can then (through the lung) invade the shoulder blade, sternum, and (through the pulmonary vein) the left atrium, with systemic circulation as the path to the whole body. Thus, combined lung metastasis in CRC patients means higher probability of bone metastasis[16-18].

This study has some limitations. The study's retrospective design and reliance on existing medical records may introduce selection bias and limit data accuracy. With only 100 patients, the sample size was small, potentially affecting the generalizability and statistical power of the findings. The study also lacked a specified follow-up duration for bone metastasis, which could influence the timing and detection of metastatic events. Additionally, the analysis did not account for potential confounding variables or variations in treatment modalities, which might affect the risk of bone metastasis. The study's focus on patients with CRC may limit the applicability of the findings to other cancer types. Furthermore, the lack of functional outcome measures means the study did not assess the effect of bone metastasis on quality of life. Despite these limitations, our findings provide valuable insights into the risk factors for bone metastasis and highlights areas for further research.

Table 4 Multiple logistic regression models analyzed the risk factors affecting postoperative bone metastasis in patients undergoing colorectal cancer surgery

Factor	Partial regression coefficient	SE	Wald	OR	95%CI	*P* value
The primary location of the tumor was a rectal cancer	1.128	0.322	17.527	2.456	1.644-3.674	< 0.001
With combined lymph node involvement	1.144	0.311	10.214	2.024	1.159-3.654	< 0.001
Combined lung metastases	1.134	0.241	14.327	3.124	2.124-5.544	< 0.001
No chemotherapy was administered after surgery	1.412	0.224	21.236	3.544	1.664-6.922	< 0.001

OR: Odds ratio; CI: Confidence interval.

CONCLUSION

Bone metastases are common in CRC patients with deeper tumor invasion, those with multiple osteolytic lesions, and those who have multiple bone metastases. The primary tumor location being the rectum, lymph node involvement, combined lung metastasis, and no postoperative chemotherapy are risk factors for postoperative bone metastasis in patients with CRC, and can contribute to the early clinical identification of the high risk of bone metastasis in these patients.

FOOTNOTES

Author contributions: Tang QY designed the study; Tang QY and Yu W contributed to the analysis of the data and writing of this article; and both authors have read and approved the final manuscript.

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Effect of rapid rehabilitation surgical nursing on patients' gastrointestinal function recovery and sleep quality after laparoscopic appendectomy

Shan-Shan Chen, Yi-Ming Gao, Xiao-Fang Yao, Qi-Qi Zhang, Kai-Long Yang, Qiao Xia, Jing Ding

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Abstract

BACKGROUND

Appendicitis is a common acute abdominal pain disorder. Laparoscopic appendectomy, a commonly used modality, is associated with less trauma and faster recovery than traditional open appendectomy. However, postoperative recovery remains an important issue that affects rehabilitation quality and surgical results.

AIM

To explore the effects of rapid rehabilitation and surgical nursing care on gastrointestinal function recovery and sleep quality among patients undergoing laparoscopic appendectomy.

METHODS

A total of 120 patients who underwent laparoscopic appendectomy at our hospital between January 2019 and March 2024 and for whom complete clinical data were available were selected. Patients were randomly assigned to two groups (n = 60 each) using the random number table method. The control group received routine nursing care, while the experimental group received rapid rehabilitation surgical nursing care; all patients continued to receive nursing care until discharge. The recovery of gastrointestinal function, length of hospital stay, complications,

Pittsburgh sleep quality index, and nursing satisfaction were compared between groups.

RESULTS

Following the implementation of effective nursing measures, the times to bowel sound recovery, first exhaust, first defecation, and first feeding were notably shorter in the study *vs* control group ($P < 0.05$). Additionally, the duration of the first postoperative activity and the length of hospital stay were significantly shorter in the study *vs* control group ($P < 0.05$). Furthermore, the study group exhibited better sleep quality than the control group ($P < 0.05$). The postoperative complication rate was significantly lower and the nursing satisfaction rate significantly higher in the study *vs* control group ($P < 0.05$).

CONCLUSION

Rapid rehabilitation surgical nursing interventions provided to patients after laparoscopic appendectomy can accelerate their postoperative recovery, reduce the occurrence of complications, and improve their sleep quality and nursing satisfaction.

Key Words: Laparoscopic appendectomy; Rapid rehabilitation surgical nursing; Gastrointestinal function recovery; Sleep quality; Nursing satisfaction

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Core Tip: To explore the effects of rapid rehabilitation surgical nursing on gastrointestinal function recovery and sleep quality in patients undergoing laparoscopic appendectomy. Rapid rehabilitation surgical nursing interventions provided to patients after laparoscopic appendectomy can accelerate their postoperative recovery, reduce the occurrence of complications, and improve their sleep quality and nursing satisfaction.

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INTRODUCTION

Appendicitis, a common surgical emergency, involves inflammation of the appendix that can be classified into early, acute, gangrenous, and chronic stages based on its progression[1]. It mainly manifests as abdominal pain in individuals aged 5-45 years, carries a risk of occurrence of 8.6% in men *vs* 6.7% in women[2], and is usually treated by surgical excision[3]. Laparoscopic appendectomy is currently the conventional approach[4]; it is typically performed after hours, features less trauma, and leads to faster recovery than traditional open appendectomy[5]. This minimally invasive technique reduces incision time and minimizes postoperative pain and complications, leading to a quicker return to normal activities[6]. However, postoperative recovery remains an important issue affecting rehabilitation quality and surgical results[7].

Conventional postoperative nursing methods usually involve bed rest and lack systematic rehabilitation intervention measures, resulting in a slow recovery period and high incidence of complications[8]. Rapid rehabilitation surgical nursing is a comprehensive nursing measure that follows evidence-based medicine standards and optimizes routine nursing interventions[9] and includes early activity, pain management, nutritional support, psychological support, and other measures aiming to promote postoperative rehabilitation, reduce the incidence of complications, and improve patient quality of life[10,11]. Rapid rehabilitation is widely administered in various clinical settings. Anal preservation surgery for rectal cancer accelerates the recovery process and reduces length of hospital stay and medical costs[11].

Rapid rehabilitation surgery is increasingly used in clinical nursing to alleviate stress, reduce postoperative pain and complications, and enhance patient quality of life while accelerating the rehabilitation process. According to previous clinical studies, patients undergoing laparoscopic appendectomy with an enhanced recovery surgery protocol have significantly shorter exhaust times, lengths of hospital stay, hospitalization costs, and pain scores than those receiving conventional therapy[5,12]. Implementing rapid rehabilitation in surgical nursing care can effectively reduce patients' postoperative stress and complications, allowing for their quicker recovery[13,14]. This finding suggests that enhanced surgical recovery regimens can significantly accelerate the recovery process, shorten the length of hospital stay, and reduce the hospitalization costs of patients with appendicitis. In addition, evidence-based nursing interventions for patients with heart failure and tumors demonstrated significant clinical effects that improved patient postoperative status and quality of life[15]. Comprehensive nursing interventions are important in post–lumbar surgery rehabilitation because they can effectively relieve pain, reduce inflammation, and improve overall recovery quality[8]. Therefore, it is important that we explore the effects of rapid rehabilitation surgical nursing on gastrointestinal function recovery and sleep quality in patients undergoing laparoscopic appendectomy.

This study aimed to explore the effects of a rapid rehabilitation surgical nursing intervention on gastrointestinal function recovery and sleep quality in patients undergoing laparoscopic appendectomy; evaluate its ability to promote postoperative rehabilitation, improve sleep quality, and reduce complication rates; and provide a basis for improving the surgical treatment effect and optimizing clinical nursing to promote the development of surgical nursing.

MATERIALS AND METHODS

Patients' general information

We retrospectively selected 120 patients who underwent laparoscopic appendectomy at our hospital between January 2019 and March 2024. The participants were randomly assigned using a random number table to the control group, consisting of 60 patients who received standard nursing care, and the study group, consisting of 60 patients who received rapid rehabilitation surgical nursing care.

Inclusion and exclusion criteria

The inclusion criteria were as follows[16]: (1) Diagnosis of appendicitis based on clinical manifestations, ultrasonography, and laboratory examination results (excluding cases of appendiceal perforation and periappendiceal abscess); (2) No contraindications for general anesthesia or laparoscopic surgery; (3) No history of mental illness but normal cognitive function; and (4) Availability of complete clinical data.

The exclusion criteria were as follows: (1) Currently pregnant or lactating; (2) Serious mental illness or psychological disorder; and (3) Severe hypertensive heart disease.

Ethical considerations

This study was approved by our institution's research ethics committee and performed in accordance with the Declaration of Helsinki and its subsequent revisions. Informed consent was obtained from all included patients.

Nursing methods

Control group: Patients in the control group received routine nursing care as follows: (1) Monitoring of vital signs (body temperature, pulse, respiration, and blood pressure); (2) timely administration of analgesics to ensure pain control; (3) Regular dressing changes to keep the wound clean and dry and avoid infection with monitoring for redness, swelling, seepage, or other abnormalities; (4) Monitoring of fluid volume and output to ensure water balance and prevent dehydration or water poisoning; (5) Gradual restoration of diet according to patient's postoperative recovery progress to avoid overeating-induced indigestion; (6) Gradual resumption of normal activities according to the doctor's advice including avoiding strenuous exercise, lifting heavy objects, and preventing wounds from splitting; and (7) Regular postoperative follow-ups including observations of wound healing, assessments of patient rehabilitation progress, and timely detection and treatment of complications.

Study group[17]: Patients in the study group received rapid rehabilitation surgical nursing interventions as follows: (1) Preoperatively, a comprehensive assessment of the patient's physical condition, chronic disease, drug use, *etc.* to ensure the creation of a more individualized care plan; (2) Formation of a team of surgeons, nurses, rehabilitation doctors, *etc.* to ensure seamless surgical and postoperative care; (3) Use of appropriate analgesic methods, such as local anesthesia or an analgesic pump, to reduce postoperative pain and promote movement and deep breathing; (4) Encouragement of early postoperative patient activity, including early awakening, walking, and simple rehabilitation activities, to help prevent complications such as deep vein thrombosis; (5) Provision of digestible nutrient-rich food to meet any special needs and monitoring of fluid intake to ensure adequate hydration; (6) Development of a personalized rehabilitation plan, including physical therapy and rehabilitation exercises, to help patients gradually regain their ability to move; (7) Implementation of appropriate infection control measures, including hand hygiene, wound care, and antibiotic use, to reduce the risk of infection; (8) Provision of psychological support to patients to meet their emotional and mental health needs; (9) Provision of regular postoperative follow-ups to monitor the patient's recovery process and identify and timely solve potential problems; and (10) Provision of relevant health education to ensure that patients and their families understand the postoperative precautions, dietary recommendations, and drug management protocols to promote patient participation in the rehabilitation process.

Observation indexes

Postoperative recovery of gastrointestinal function included time to bowel sound recovery, first defecation, first exhaust, and first feeding as well as length of hospital stay.

Sleep quality[18]: The Pittsburgh sleep quality index (PSQI), which was used to evaluate patients' sleep quality, encompasses seven dimensions (total of 19 items): Sleep efficiency, quality, disturbances, duration, and latency; hypnotic medication use; and daytime dysfunction. A four-point scoring system was employed (maximum score, 21 points), with higher scores indicating poorer sleep quality. The scale demonstrated good reliability and validity as evidenced by a Cronbach's α coefficient of 0.710.

Postoperative complications: Postoperative complications included incisional infection, intestinal obstruction, adhesions, and abscesses.

Nursing satisfaction[19]: Satisfaction with the nursing care was assessed using a custom-made questionnaire developed at our hospital. A score of < 60 was considered "unsatisfactory," indicating that patients believed that the clinical nursing care had no significant effect on their psychological status, comfort level, and pain degree; a score of 60-85 was considered "basically satisfied," indicating that the clinical nursing care somewhat improved their own psychological condition, comfort, and pain degree; and a score of > 85 was considered "very satisfied," indicating that the clinical nursing work significantly improved their psychological condition, comfort, and pain degree. Total satisfaction rate = [(basically satisfied + satisfied) cases/total cases] × 100.

Statistical analysis

Data analyses were performed using SPSS Statistics for Windows (version 26.0; IBM, Armonk, NY, United States). Continuous variables are presented as mean ± SD and were compared between groups using independent *t*-tests to identify significant differences. Categorical variables are shown as count and percentage, *n* (%) and were assessed using the χ^2 test for intergroup comparisons. Statistical significance was set at $P < 0.05$.

RESULTS

General data comparison

The patients' baseline characteristics were comparable between groups ($P > 0.05$) (Table 1). The study group included 35 men and 25 women with a median age (25^{th}-75^{th} interquartile range) of 39 (33-37) years and a mean disease duration of 4.45 ± 0.64 hours. The control group included 33 men and 27 women with a median age (25^{th}-75^{th} interquartile range) of 38 (32-38) years and a mean disease duration of 4.51 ± 0.70 hours.

Gastrointestinal function recovery and length of hospital stay

After effective nursing measures were provided, bowel sound recovery, first exhaust, first defecation, and first feeding times were significantly shorter in the intervention *vs* control group ($P < 0.05$). The first postoperative activity time and length of hospital stay were also significantly shorter in the intervention *vs* control group ($P < 0.05$) (Figure 1).

Sleep quality

All PSQI and total scores were lower in the study *vs* control group ($P < 0.01$) (Figure 2), suggesting that patients in the control group had poorer sleep quality than those in the study group.

Postoperative complications

The incidence of postoperative complications was significantly lower in the study [3.3% (2/60)] *vs* control [11.7% (7/60)] group ($P < 0.01$) (Figure 3A).

Nursing satisfaction

The nursing satisfaction rate was significantly higher in the study [96.7% (58/60)] *vs* control group [78.3% (47/60)] ($P < 0.05$) (Figure 3B).

DISCUSSION

The rapid rehabilitation surgical care model uses an evidence-based medical approach to accelerate postoperative patient recovery and improve clinical outcomes. This model has been widely used with good results in laparoscopic surgery in various clinical departments[20]. Rapid rehabilitation surgical nursing protocols reportedly promote the recovery of gastrointestinal function, accelerate postoperative rehabilitation, and reduce complication rates[21]. Moreover, the use of rapid rehabilitation surgical nursing practices for patients undergoing laparoscopic myomectomy was proven effective at decreasing intraoperative bleeding, shortening the first postoperative exhaust time and length of hospital stay, and decreasing the bladder irritation rate[20]. These findings indicate that the rapid rehabilitation surgical nursing model enhances patient satisfaction and significantly reduces the incidence of postoperative complications. Therefore, it has important clinical application value for improving postoperative recovery and clinical outcomes[22].

These results showed that, after the nursing intervention, bowel sound recovery, first exhaust, first defecation, and first feeding times were significantly shorter in the study *vs* control group ($P < 0.05$). These findings suggest that rapid rehabilitation surgical nursing care can effectively promote functional intestinal reconstruction and shorten the recovery time by reducing postoperative intestinal dysfunction. Moreover, the duration of the first postoperative mobilization and length of hospitalization were significantly shorter in the study *vs* control group ($P < 0.05$), further supporting the important role of the rapid rehabilitation nursing strategy in reducing the length of hospitalization and accelerating the recovery process, a finding that is consistent with previous research results[23].

Improved sleep is another notable outcome of rapid rehabilitation among surgical nurses. The mean PSQI score was significantly lower in the study *vs* control group ($P < 0.01$), indicating that its use improved patients' physical and mental health recovery. The efficacy of this approach was validated in several previous studies. For example, patients who received rapid rehabilitation nursing care after radical gastrectomy showed significantly improved gastrointestinal

Table 1 Comparison of general data between the two groups, *n* (%)

Index	Study group (*n* = 60)	Control group (*n* = 60)	*P* value
Median age (25^{th}-75^{th} IQR) (years)	39 (33-37)	38 (32-38)	0.532
Sex			0.723
Male	35 (58.3)	33 (55.0)	
Female	25 (41.7)	27 (45.0)	
BMI (kg/m^2)	23.23 ± 3.05	23.26 ± 3.24	0.512
Mean duration of disease (h)	4.45 ± 0.64	4.51 ± 0.70	0.964
Pathological types		0.737	
Acute pure appendicitis	36 (60.0)	34 (56.7)	
Acute purulent appendicitis	24 (40.0)	26 (43.3)	
Smoking history (*n*)		0.182	
Yes	16 (26.7)	18 (30.0)	
No	44 (73.3)	42 (70.0)	
Drinking history (*n*)		0.173	
Yes	20 (33.3)	22 (36.7)	
No	40 (66.7)	38 (63.3)	

BMI: Body mass index.

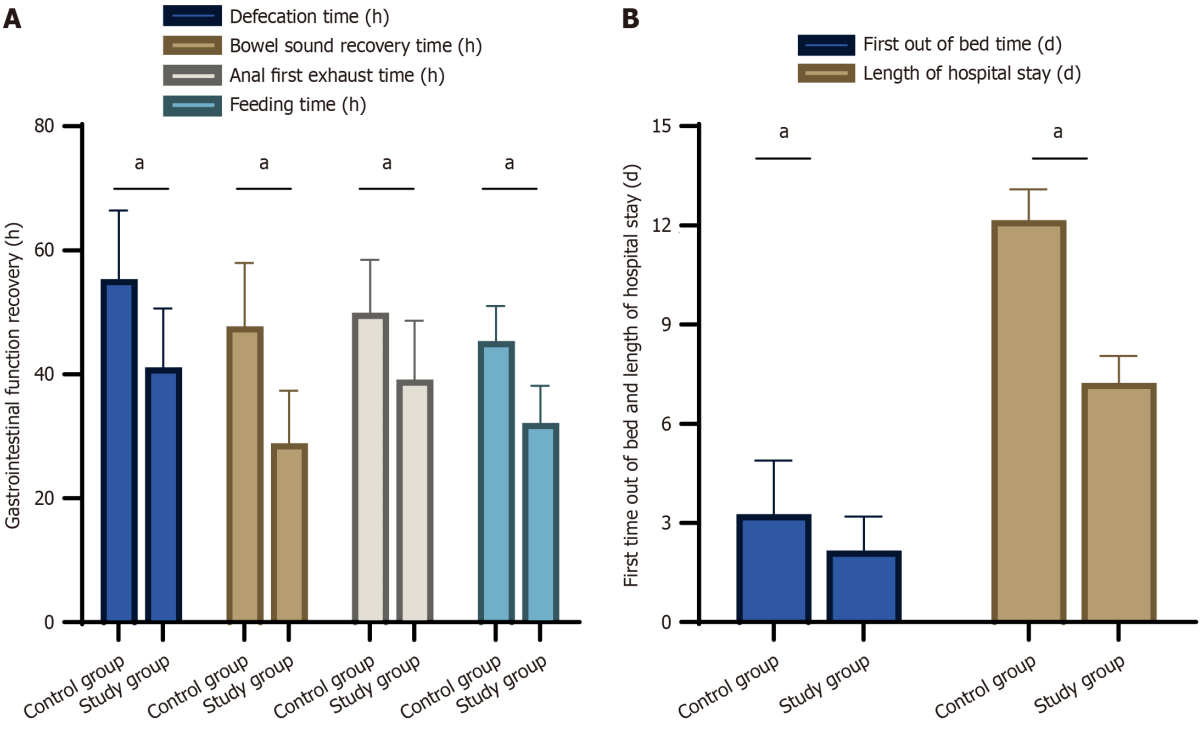


Figure 1 Comparison of gastrointestinal function recovery and hospital stay between the two groups. A: Comparison of gastrointestinal function recovery between the two groups; B: The first time out of bed and the length of hospital stay were compared between the two groups. $^aP < 0.05$ *vs* control.

function and fewer complications[21]. Moreover, rapid rehabilitation nursing care provided to patients undergoing laparoscopic myomectomy results in a lower incidence of postoperative complications and a higher rate of patient satisfaction[23]. These findings suggest that rapid rehabilitation care accelerates the physical recovery of patients and improves their overall quality of life and mental health.

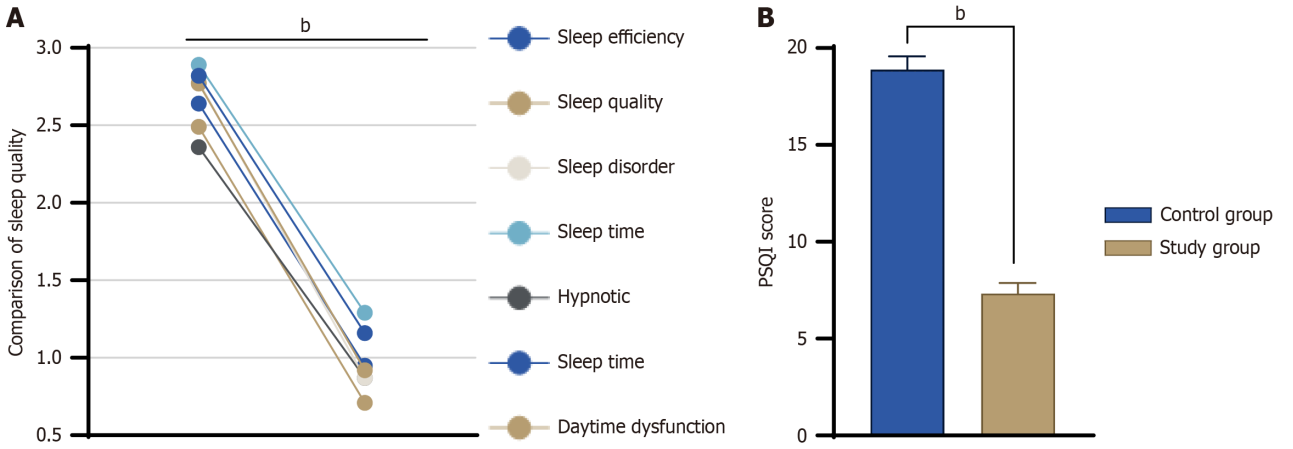


Figure 2 Comparison of Pittsburgh sleep quality index scores and total scores after surgery between the two groups. A: Comparison of Pittsburgh sleep quality index (PSQI) scores between the two groups; B: The PSQI total scores were compared between the two groups. $^{b}P < 0.01$ *vs* control.

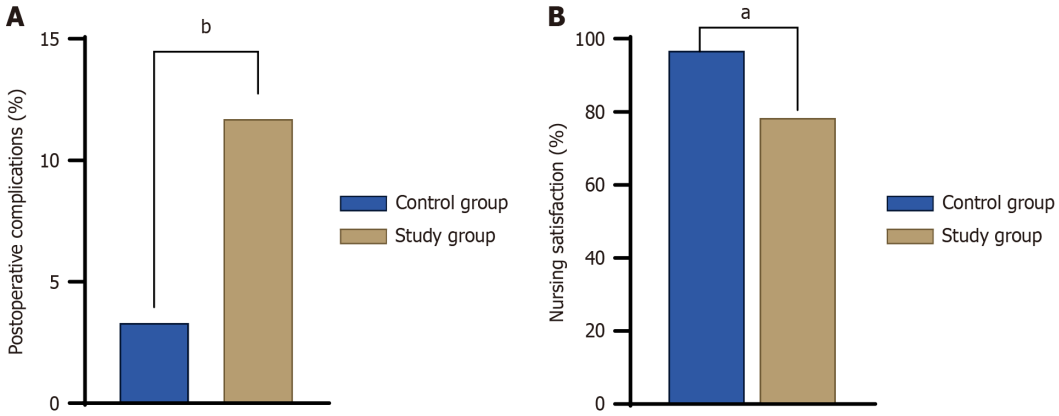


Figure 3 Comparison of postoperative complications and nursing satisfaction between the two groups. A: Postoperative complications; B: Nursing satisfaction. $^{a}P < 0.05$ *vs* control; $^{b}P < 0.01$ *vs* control.

The postoperative complication rate was significantly lower in the study (3.3%) *vs* control (11.7%) group ($P < 0.01$). These findings suggest that rapid rehabilitation nursing care can significantly reduce the incidence of postoperative complications. Rapid rehabilitation nursing care helps reduce patient anxiety and stress by using scientific nursing measures and personalized patient-centered programs, thereby reducing the occurrence of postoperative complications.

The mechanisms by which rapid rehabilitation surgical nursing enhance gastrointestinal function and sleep quality require further investigation. Physiologically, improved gastrointestinal function may be linked to earlier mobilization and dietary interventions that stimulate bowel activity. Psychologically, reducing anxiety through effective communication and supportive care can improve the sleep quality and overall patient satisfaction. Finally, the nursing satisfaction rate was significantly higher in the study [96.7% (58/60)] *vs* control [78.3% (47/60)] group ($P < 0.05$). This finding further supports the efficacy of the rapid rehabilitation nursing model[21].

Limitations

This single-center retrospective study has certain limitations. First, its relatively small sample size ($n = 120$) may have affected the generalizability and reliability of the statistical results. Although the results were significant, validation in a larger sample size is necessary to ensure that these findings are applicable across hospitals and populations. Second, the study's single-center design may have led to selection bias, as variations in nursing practices, patient population characteristics, and the availability of medical resources in different hospitals may have affected the nursing outcomes. Therefore, future studies should adopt a multicenter design to increase sample diversity and representativeness, thereby improving the external validity of our findings. Third, its retrospective design influenced the results to some extent because missing or incorrectly recorded patient data may have affected the accuracy of the results. To overcome this problem, future studies should consider using prospective randomized controlled designs to enhance confidence in the results. Finally, although this study focused on postoperative improvements in gastrointestinal function and sleep quality, other potential influencing factors, such as the patient's psychological state, social support system, and follow-up care arrangements, require further exploration in future studies. Therefore, future studies will require larger sample sizes and multicenter design to further verify the efficacy of rapid rehabilitation surgical nursing care and provide a solid foundation for development in this field.

CONCLUSION

This study demonstrated that rapid rehabilitation surgical nursing care effectively supports patients after laparoscopic appendectomy by enhancing their gastrointestinal recovery, sleep quality, and nursing satisfaction while reducing complications. These findings are crucial to the advancement of modern surgical nursing. Future larger multicenter studies are needed to confirm its effectiveness and feasibility.

FOOTNOTES

Author contributions: Chen SS, Gao YM was the guarantor and designed the study; Chen SS participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Yao XF, Zhang QQ, Yang KL, Xia Q, Ding J revised the article critically for important intellectual content. Chen SS and Gao YM contributed equally to this work as co-first authors.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Early prediction of anastomotic leakage after rectal cancer surgery: Onodera prognostic nutritional index combined with inflammation-related biomarkers

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Abstract

BACKGROUND

Anastomotic leakage (AL) is a serious complication following rectal cancer surgery and is associated with increased recurrence, mortality, extended hospital stays, and delayed chemotherapy. The Onodera prognostic nutritional index (OPNI) and inflammation-related biomarkers, such as the neutrophil-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been studied in the context of cancer prognosis, but their combined efficacy in predicting AL remains unclear.

AIM

To investigate the relationships between AL and these markers and developed a predictive model for AL.

METHODS

A retrospective cohort study analyzed the outcomes of 434 patients who had undergone surgery for rectal cancer at a tertiary cancer center from 2016 to 2023. The patients were divided into two groups on the basis of the occurrence of AL: One group consisted of patients who experienced AL (n = 49), and the other group did not (n = 385). The investigation applied logistic regression to develop a risk prediction model utilizing clinical, pathological, and laboratory data. The efficacy of this model was then evaluated through receiver operating charac-

teristic curve analysis.

RESULTS

In the present study, 11.28% of the participants (49 out of 434 participants) suffered from AL. Multivariate analysis revealed that preoperative levels of the OPNI, NLR, and PLR emerged as independent risk factors for AL, with odds ratios of 0.705 (95%CI: 0.641-0.775, P = 0.012), 1.628 (95%CI: 1.221-2.172, P = 0.024), and 0.994 (95%CI: 0.989-0.999, P = 0.031), respectively. These findings suggest that these biomarkers could effectively predict AL risk. Furthermore, the proposed predictive model has superior discriminative ability, as demonstrated by an area under the curve of 0.910, a sensitivity of 0.898, and a specificity of 0.826, reflecting its high level of accuracy.

CONCLUSION

The risk of AL in rectal cancer surgery patients can be effectively predicted by assessing the preoperative levels of serum nutritional biomarkers and inflammatory indicators, emphasizing their importance in the preoperative evaluation process.

Key Words: Platelet-to-lymphocyte ratio; Neutrophil-to-lymphocyte ratio; Postoperative anastomotic leakage; Ondera prognostic nutritional index; Rectal cancer surgery

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Core Tip: This study introduces a novel approach to predict anastomotic leakage (AL) risk in colorectal cancer (CRC) patients. It explored the combined application of the Onodera prognostic nutritional index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio. The results demonstrate that this combination significantly enhances the accuracy of AL prediction, providing a more reliable tool for personalized management of patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC) is a significant digestive system malignancy, with an estimated 1.9 million new cases reported worldwide in 2020 and approximately 935000 deaths linked to the disease. CRC is the third most frequently diagnosed cancer and the second primary contributor to cancer-related deaths, and these statistics emphasize the extensive health burden posed by CRC[1].

CRC treatment primarily involves surgical interventions, radiotherapy, chemotherapy, and targeted therapy. With advancements in surgical methods, such as improved resection and anastomosis techniques and the utilization of modern instruments, surgery continues to be the cornerstone of CRC management. While these advancements have enhanced the prospects for successful radical treatment, complications from surgery are still a concern. Among them, anastomotic leakage (AL) is a major postoperative complication that significantly contributes to abdominal infections, sepsis, extended hospitalization, high reoperation rates, and increased short- and long-term morbidity and mortality[2,3]. Consequently, it is crucial for medical professionals to identify the risk factors that contribute to AL following colorectal surgeries.

The precise cause of AL remains elusive; however, current research indicates that it likely arises from a convergence of multiple elements, including advanced age, obesity, smoking, alcohol intake, and surgeon experience. The duration of colorectal surgery and patient-related factors, such as nutritional state, inflammation, and immune function, also significantly contribute to the risk of AL[4]. Researchers have identified several biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio, which are indicators of the AL risk[5]. Furthermore, new indices have been introduced in recent years, such as the systemic immune-inflammatory index (SII), the Onodera prognostic nutritional index (OPNI), the pan-immune inflammatory value, and the systemic inflammatory response index, all of which have demonstrated associations with survival rates in various malignancies[6-8].

Timely detection and prevention are vital for reducing the likelihood of potential AL. Early identification and assessment of the severity of this complication play a decisive role in lowering postoperative mortality and enhancing patient care quality. Considering the link between AL and factors such as nutrition, inflammation, and immunity, investigating markers that could be integrated into standard blood tests to predict AL in colorectal surgery patients with CRC might aid in predicting and hindering AL development, ultimately contributing to improved treatment outcomes.

The objective of this study was to create an efficient predictive model of AL, focusing on nutritional and inflammation-related biomarkers, with the intent of precisely evaluating the risk of AL in patients after rectal cancer surgery. This model offers a straightforward and accurate assessment tool for clinicians, ultimately improving patient management strategies and enhancing overall survival.

MATERIALS AND METHODS

General information of patients

Employing the Cochran formula, we estimated the required sample size by considering a 10% event rate, a 5% margin of error, and a 95% confidence level. This computation led to a required sample size of 139 patients. Over the course of the study, from January 2016 to December 2023, a total of 434 patients with rectal cancer were recruited from the Cancer Hospital of Xinjiang Medical University, significantly surpassing the initially calculated sample size. The eligibility criteria for participation were as follows: (1) Had a confirmed diagnosis of rectal cancer; (2) Were 18 years of age or older; (3) Had undergone radical rectal cancer surgery; and (4) Had complete preoperative data and examination records available. Individuals were excluded from the study if they: (1) Had distant metastasis at the time of enrollment; (2) Had received radiotherapy or chemotherapy before surgical intervention; (3) Had significant preexisting complications; (4) Had undergone Miles or Hartman surgery without anastomosis; or (5) Were diagnosed with nonprimary rectal cancer. The participating patients provided written informed consent after having been fully apprised of the study details. This research was conducted ethically after receiving clearance from the Ethics Committee of Xinjiang Medical University Cancer Hospital (Approval No: K-2024170).

Data collection

The patient data utilized in this study were obtained solely from our electronic information system, which provides comprehensive information on participants, including their age, gender, body mass index, medical history of diabetes mellitus and hypertension as comorbidities, smoking and alcohol intake, and preoperative factors such as intestinal obstruction and tumor specificity (T stage, N stage, TNM stage, tumor differentiation, neural infiltration, and choroidal invasion). We also recorded various hematological parameters, including white blood cell (WBC), hemoglobin (Hb), platelet (Plt), lymphocyte (LYM), neutrophil, and monocyte (MONO) counts. To facilitate deeper analysis, we derived additional markers: OPNI = albumin (ALB) + 5 × MONO count (10^9/L); NLR = neutrophil count (10^9/L)/LYM count (10^9/L;) and PLR = Plt count (10^9/L)/LYM count (10^9/L).

Diagnosis and definition of AL

Patients were classified into two categories based on the development of AL within two weeks postsurgery: The AL group, which included 49 patients, and the non-AL group, which consisted of 385 patients. AL was diagnosed according to the following criteria: (1) The presence of unexplained abdominal pain, bloating, or an uncontrolled postoperative fever, either with or without signs of peritoneal irritation; (2) Alterations in drainage patterns, characterized by a substantial rise in pelvic drainage volume, often containing gas, pus, or feces; (3) Digital rectal exam revealing a palpable anastomosis leak; (4) Imaging studies that revealed contrast medium extravasation, bowel discontinuity, or the presence of air pockets adjacent to the anastomosis; and (5) Significant laboratory results showing elevated WBC count, an increased neutrophil count, and a higher than normal neutrophil percentage[9].

Statistical analysis

Continuous variable data are presented as median values with their respective quartiles (Q1 to Q3). Statistical analysis was conducted using IBM SPSS software, version 26.0, and group differences were assessed *via* nonparametric tests, specifically the Wilcoxon rank-sum test. For categorical variables, data are shown as frequencies (n) and corresponding percentages (%). To analyze categorical data across different groups, we employed Fisher's exact test when the expected frequency was less than 5; otherwise, the χ^2 test was used. To examine the risk factors associated with postoperative AL, we applied both univariate and multivariate logistic regression models. The diagnostic efficacy of serum nutritional indices in predicting postoperative AL was assessed through receiver operating characteristic (ROC) curve analysis. In the R platform, a predictive model was developed with the "rms" package to construct nomograms[10,11]. The performance of various serum nutritional and inflammatory markers, as well as the predictive models, was evaluated by contrasting their sensitivity, specificity, and area under the curve (AUC) values. The predictive model's calibration was assessed and depicted graphically through a calibration analysis utilizing the "rms" package to ensure visual representation of the model's performance. A statistically significant difference was considered to be a P value less than 0.05.

RESULTS

Clinical and pathological features of AL and non-AL patients

In a study involving 434 patients who had undergone rectal cancer surgery, 49 participants (accounting for 11.28% of the group) experienced postoperative AL. A comparison of the clinical and pathological features between patients with AL (n = 49) and those without AL (n = 385) is shown in Table 1. The baseline characteristics of the entire patient group (n = 434) were assessed across diverse variables. The prevalence of AL was significantly greater among males than females (P =

Table 1 Comparison of clinical data, *n* (%)

Characteristic	Anastomotic leakage group (*n* = 49)	No anastomotic leakage group (*n* = 385)	Statistic	*P* value
Age			0.96	0.3282[1]
< 60	173 (44.9)	18 (37.5)		
≥ 60	212 (55.1)	30 (62.5)		
Gender			3.66	0.0562[1]
Male	220 (57.1)	35 (71.4)		
Female	165 (42.9)	14 (28.6)		
BMI				0.2623[2]
< 18.5	11 (2.9)	4 (8.2)		
18.5-24	169 (43.9)	22 (44.9)		
24-28	159 (41.3)	19 (38.8)		
≥ 28	46 (11.9)	4 (8.2)		
Smoking			0.87	0.3522[1]
No	268 (69.8)	31 (63.3)		
Yes	116 (30.2)	18 (36.7)		
Drinking			1.61	0.2042[1]
No	308 (80.2)	43 (87.8)		
Yes	76 (19.8)	6 (12.2)		
History of hypertension			2.03	0.1552[1]
No	295 (76.6)	33 (67.3)		
Yes	90 (23.4)	16 (32.7)		
Cardiac insufficiency				0.1333[2]
No	371 (96.4)	45 (91.8)		
Yes	14 (3.6)	4 (8.2)		
History of diabetes			3.97	0.0462[1]
No	330 (85.7)	47 (95.9)		
Yes	55 (14.3)	2 (4.1)		
History of abdominal surgery			0.48	0.4872[1]
No	289 (75.1)	39 (79.6)		
Yes	96 (24.9)	10 (20.4)		
ASA				0.4623[2]
1-2	369 (95.8)	46 (93.9)		
3-4	16 (4.2)	3 (6.1)		
Bowel obstruction				0.3133[2]
No	366 (95.1)	45 (91.8)		
Yes	19 (4.9)	4 (8.2)		
Black stool			0.04	0.8392[1]
No	163 (42.3)	20 (40.8)		
Yes	222 (57.7)	29 (59.2)		
Differentiated degree				> 0.9993[2]
Poorly	33 (8.6)	4 (8.2)		
Moderately	317 (82.3)	41 (83.7)		

Well	35 (9.1)	4 (8.2)		
Nerve invasion			1.01	0.3142[1]
Negative	320 (83.3)	38 (77.6)		
Positive	64 (16.7)	11 (22.4)		
Intravascular tumor emboli			0.00	0.9552[1]
Negative	313 (81.3)	40 (81.6)		
Positive	72 (18.7)	9 (18.4)		
T stage				0.4643[2]
T1	20 (5.2)	2 (4.2)		
T2	59 (15.3)	4 (8.3)		
T3	281 (73.0)	37 (77.1)		
T4	25 (6.5)	5 (10.4)		
N stage				0.5853[2]
N0	224 (58.2)	31 (63.3)		
N1	101 (26.2)	9 (18.4)		
N2	56 (14.5)	9 (18.4)		
N3	4 (1.0)	0 (0.0)		
Tumor stage			0.19	0.6592[1]
1-2	223 (57.9)	30 (61.2)		
3-4	162 (42.1)	19 (38.8)		

[1]Pearson's χ^2 test.
[2]Fisher's exact test.
BMI: Body mass index; ASA: American Society of Anesthesiologists.

0.056), with a male-to-female ratio tending toward significance in the AL group. Notably, a history of diabetes mellitus was significantly associated with the development of AL (P = 0.046), suggesting that individuals with diabetes are more likely to develop AL. This finding implies that those with diabetes mellitus preoperatively might necessitate a more conservative surgical approach. There were no statistically significant differences in smoking habits, alcohol use, or history of hypertension between the two groups. Importantly, diabetes, along with other factors, shaped the demographic and clinical profiles of the study participants. They offer valuable insights into the variables that might influence the study's outcome measures, even though smoking, alcohol consumption, and hypertension did not show any notable disparities between the groups. Nevertheless, diabetes has emerged as a key parameter with implications for the results under examination.

Comparison of serological and hematological correlates

Table 2 outlines the baseline characteristics of the 434 participants, highlighting the disparities in laboratory indices between the two groups. There were no significant differences in WBC, Plt, or neutrophil counts, or serum carcinoembryonic antigen or carbohydrate antigen 199 levels between the groups with and without AL. However, substantial variations were noted in the Hb concentration, MONO, LYM count, NLR and PLR. All these parameters exhibited statistically notable disparities, with P values less than 0.001, indicating significant differences between the AL group and the non-AL group. These findings imply that nutritional status and inflammation-related biomarkers, as represented by the OPNI, are distinct between the groups, indicating that AL status is likely to be correlated with various hematological and serological markers. These findings suggest a potential influence of systemic nutritional status and the immune response on the occurrence of AL.

Risk factor analysis of AL after rectal cancer surgery

Rectal cancer patients' risk factors for AL were assessed *via* univariate and multivariate logistic regression analyses. The preliminary univariate analysis, summarized in Table 3, identified seven noteworthy factors with ORs: Hb at 0.980 (95%CI: 0.969-0.991, P < 0.001), LYM count at 0.105 (95%CI: 0.048-0.231, P < 0.001), MONO at 6.567 (95%CI: 1.659-25.995, P = 0.007), neutrophil count with an OR of 1.312 (95%CI: 1.129-1.523, P < 0.001), NLR at 0.702 (95%CI: 0.642-0.768, P < 0.001), PLR at 1.838 (95%CI: 1.47-2.298, P < 0.001), and OPNI with an OR of 1.008 (95%CI: 1.004-1.012, P < 0.001). However, subsequent multivariate logistic regression revealed that the OPNI, NLR, and PLR were the sole independent predictors of AL risk, with adjusted ORs of 0.705 (95%CI: 0.641-0.775, P = 0.012), 1.628 (95%CI: 1.221-2.172, P = 0.024), and

Table 2 Haematological and serological indicators, *n* (%)

Indicators	Anastomotic leakage group (*n* = 49)[1]	No anastomotic leakage group (*n* = 385)[1]	Statistic	*P* value
WBC	6.00 (5.18, 7.29)	6.39 (4.63, 7.87)	9333.00	0.905[2]
Hb	135 (120, 148)	120 (103, 138)	12738.00	< 0.001[2]
Plt	244 (199, 292)	225 (195, 302)	9945.00	0.536[2]
LYM	1.83 (1.49, 2.23)	1.34 (1.13, 1.64)	14667.50	< 0.001[2]
NE	3.59 (2.88, 4.35)	4.05 (2.84, 5.76)	7957.50	0.075[2]
MONO	0.44 (0.34, 0.55)	0.51 (0.39, 0.64)	7374.00	0.013[2]
OPNI	50.5 (47.4, 53.2)	42.5 (39.3, 45.6)	16750.50	< 0.001[2]
NLR	1.94 (1.46, 2.59)	3.20 (2.03, 4.22)	4799.00	< 0.001[2]
PLR	131 (101, 173)	179 (123, 251)	5934.50	< 0.001[2]
CEA (%)			2.123	0.145[3]
Normal	238 (61.8)	25 (51.0)		
High	147 (38.2)	24 (49.0)		
CA199 (%)			0.002	0.965[3]
Normal	284 (73.8)	36 (73.5)		
High	101 (26.2)	13 (26.5)		

[1]Median (IQR).
[2]Wilcoxon rank sum test.
[3]Pearson's χ^2 test.
WBC: White blood cells; Hb: Hemoglobin; Plt: Platelets; LYM: Lymphocytes; NE: Neutrophils; MONO: Monocytes; OPNI: Onodera prognostic nutrition index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199.

Table 3 Analysis of risk factors for anastomotic leakage

Variables	Univariate					Multivariate				
	β	*SE*	*Z*	*P* value	OR (95%CI)	*β*	*SE*	*Z*	*P* value	OR (95%CI)
Hb	-0.021	0.006	-3.634	< 0.001	0.980 (0.969-0.991)	0.001	0.008	0.127	0.899	1.001 (0.986-1.016)
LYM	-2.251	0.400	-5.625	< 0.001	0.105 (0.048-0.231)	0.455	0.743	0.613	0.540	0.634 (0.148-2.719)
MONO	1.882	0.702	2.681	0.007	6.567 (1.659-25.995)	1.109	1.119	0.991	0.322	3.031 (0.338-27.160)
NE	0.271	0.076	3.556	< 0.001	1.312 (1.129-1.523)	0.150	0.212	0.710	0.478	0.860 (0.568-1.303)
OPNI	-0.354	0.045	-7.781	< 0.001	0.702 (0.642-0.768)	-0.350	0.048	-7.227	< 0.001	0.705 (0.641-0.775)
NLR	0.609	0.114	5.337	< 0.001	1.838 (1.470-2.298)	0.488	0.147	3.317	< 0.001	1.628 (1.221-2.172)
PLR	0.008	0.002	4.348	< 0.001	1.008 (1.004-1.012)	-0.006	0.003	-2.026	0.043	0.994 (0.989-0.999)

Hb: Hemoglobin; LYM: Lymphocytes; MONO: Monocytes; NE: Neutrophils; OPNI: Onodera prognostic nutrition index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

0.994 (95%CI: 0.989-0.999, P = 0.031), respectively. Notably, the statistical relevance of Hb, LYM, MONO, and neutrophils disappeared in the multivariate assessment, suggesting possible moderation by other variables. Diabetes history was not significantly linked to AL risk in univariate assessments and was not significantly associated with AL risk in multivariate evaluations.

Construction and comparison of AL models

This research focused on assessing the predictive accuracy of three preoperative serum biomarkers-the OPNI, NLR, and PLR-in determining the probability of AL after laparoscopic surgical procedures. ROC curve analysis revealed that a preoperative OPNI level less than 46.60 had an AUC of 0.888 (95%CI: 0.845-0.950), corresponding to a sensitivity of 83.7% and a specificity of 81.6%. An NLR threshold of 2.98 exhibited an AUC of 0.746 (95%CI: 0.660-0.817), indicating 61.2%

sensitivity and 84.4% specificity. The optimal cutoff for the PLR was 158.15, which was associated with an AUC of 0.686 (95%CI: 0.601-0.763), along with a sensitivity and specificity of 61.2% and 69.1%, respectively. Notably, when all three biomarkers (OPNI, NLR, and PLR) were combined for AL prediction, the composite AUC increased to 0.910 (95%CI: 0.900-0.929), suggesting a sensitivity of 89.8% and a specificity of 82.6%. These results suggest that assessing all three biomarkers concurrently is more advantageous than evaluating them independently, as visualized in Figure 1.

Using multivariate logistic regression analysis, we developed a predictive model for the risk of AL in patients after rectal cancer surgery. This model was based on three independent risk factors: The OPNI, NLR, and PLR. As depicted in Figure 2, this model exhibits robust predictive accuracy, as demonstrated by ROC curve analysis. The model boasts an impressive AUC of 0.910 (95%CI: 0.864-0.956), as depicted in Figure 3A, indicating superior discriminative ability. The predictive model's calibration was evaluated through a calibration plot (Figure 3B), which displayed an almost perfect alignment with the 45-degree reference line, reflected by a fit index of 0.820. This alignment underscores the high level of consistency between the predicted and observed AL rates. To ascertain the clinical relevance of the model, we employed decision curve analysis (DCA), as illustrated in Figure 4. DCA is an intuitive and effective tool that helps clinicians judge when to use model-generated risk by comparing the net benefit of the model at different decision threshold scores.

DISCUSSION

Rectal cancer ranks among the most prevalent cancers globally, with surgery serving as the primary therapeutic approach for this disease. The goal of this procedure is the complete excision of the tumor, along with the associated lymphatic bed and any adjacent compromised organs. Over time, surgical techniques have significantly advanced; however, the risk of AL persists. AL is a particularly severe postoperative complication that significantly affects patients, their families, and society at large. It can lead to early reoperations to address complications such as infections and leaks, resulting in increased hospitalization periods, diminished quality of life for patients, and considerable economic strain on both individuals and health care systems. Despite the maturity of surgical methods, the challenge of preventing AL remains.

AL is another factor that increases the rate of recurrence and mortality, and it hinders or delays the administration of adjuvant chemotherapy. A meta-analysis reviewed 14 studies evaluating the impact of AL on a total of 11353 oncology patients and revealed that AL leads to worse overall survival and reduced cancer-specific survival rates[12]. AL usually develops within 5-7 days after surgery. Timely diagnosis and intervention for AL pose significant challenges because patients often exhibit mild symptoms when they first present. Consequently, detecting AL at an early stage is highly important for improving the prognosis of rectal cancer patients, thereby decreasing hospitalization duration and minimizing health care expenses.

Rectal cancer patients with malnutrition are at increased risk of experiencing postoperative AL due to delayed wound healing, weakened immunity, and increased susceptibility to infection. Nutrition significantly impacts the speed of recovery after surgery, the long-term prognosis, and the probability of postoperative complications. Among the markers of malnutrition, low ALB levels are particularly common, with depleted levels often indicating malnutrition. A robust body of research clearly demonstrated a correlation between preoperative ALB levels and the incidence of postoperative complications, particularly AL[13,14]. The immune system's health also plays a pivotal role in shaping cancer patients' clinical outcomes[15]. To encompass both nutritional status and immune function, the OPNI is used, which is calculated on the basis of serum ALB levels and LYM counts[16]. The OPNI has been shown to be effective in predicting postoperative complications and survival outcomes in various types of cancer, including CRC[17-19]. In a 2022 meta-analysis, CRC patients with a high OPNI demonstrated superior OS rates compared with those with a low OPNI[2]. Our study echoes these findings, as we observed a significant disparity in OPNI levels between patients in the AL group and those in the non-AL group. These findings suggest that the OPNI could serve as a predictive biomarker for postoperative AL in rectal cancer patients. This may be because malnutrition suppresses the immune response and delays wound healing.

Hypoalbuminemia is a common manifestation of malnutrition, and ALB plays a key role in maintaining immune function and the anti-inflammatory response. Low ALB levels may lead to decreased immunity and an excessive inflammatory response in the postoperative period, thereby increasing the risk of AL. Therefore, preoperative assessment of a patient's nutritional status and immune function *via* the OPNI can help identify high-risk patients and provide a basis for postoperative rehabilitation and the prevention of complications.

The NLR, a concept first introduced by Zahorec[20], has gained recognition as a crucial indicator of systemic inflammation in the field of critical care medicine. The NLR is acknowledged as a crucial parameter for predicting disease outcomes, as it surpasses the individual predictive strength of WBC, neutrophil, or LYM counts in evaluating inflammatory conditions[21,22]. Comprehensive studies have established that an increased NLR is consistently associated with increased frequencies of postoperative complications and reduced survival odds in patients with CRC[5,23-25]. Notably, it is associated with an increased likelihood of AL following rectal cancer surgery. Importantly, Miyakita *et al*[26] reported that rectal cancer patients with a preoperative NLR of 2.21 or more had strikingly greater odds (4.51 times) of experiencing postoperative AL ($P = 0.0329$).

While the OPNI, NLR, and PLR have demonstrated promising predictive value for AL, it is essential to compare these markers with commonly used predictors such as C-reactive protein (CRP) and ALB. CRP has been well established as a reliable predictor of AL in patients who have undergone colorectal surgery. A systematic review and meta-analysis revealed that the CRP level had an AUC ranging from 0.706 to 0.910 in the prediction of AL, with improved predictive accuracy when measured perioperatively[27]. Similarly, Messias *et al*[28] highlighted the utility of the CRP level in excluding AL after colorectal surgery, with an AUC within this range. Additionally, Choi *et al*[29] reported that CRP levels could predict AL in patients with enhanced recovery after surgery. On the other hand, the level of ALB, an

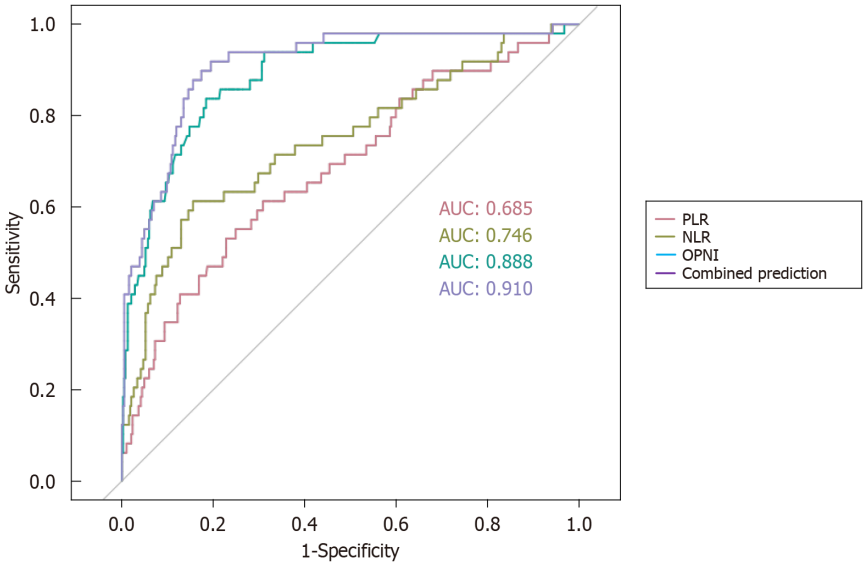


Figure 1 Area under the curve of the Onodera prognostic nutritional index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and combined prediction. OPNI: Onodera prognostic nutritional index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; AUC: Area under the curve.

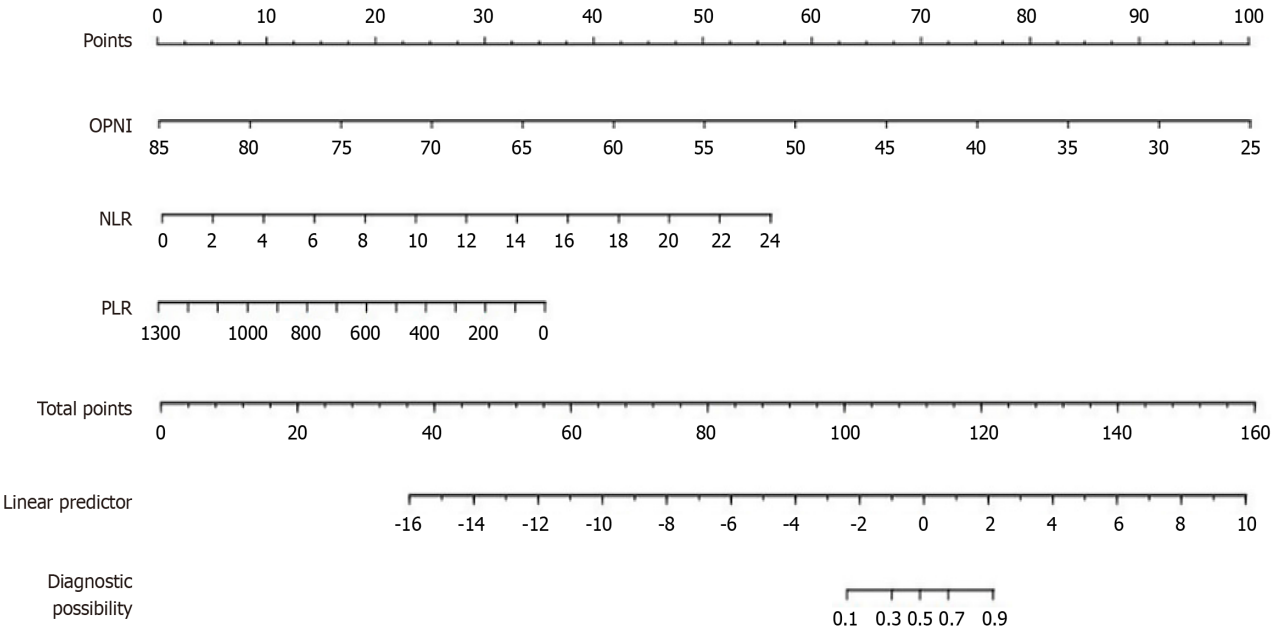


Figure 2 Nomogram for predicting postoperative anastomotic leakage in patients with rectal cancer. OPNI: Onodera prognostic nutritional index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

important marker of nutritional status, has also been linked to postoperative complications. In their study, Shimura and colleagues reported that serum ALB levels measured during the perioperative period could effectively predict the occurrence of AL in patients who underwent curative surgery for CRC. Their findings revealed an AUC ranging from 0.675 to 0.832[30]. Hu *et al*[31] further confirmed that relative decreases in the serum ALB concentration are predictive of AL in female patients after sphincter-preserving rectal surgery. In our study, the combined use of the OPNI, NLR, and PLR resulted in a superior AUC of 0.910, which outperformed CRP and ALB as predictive tools for AL. Our model achieved a high sensitivity (89.8%) and specificity (82.6%), emphasizing the comprehensive advantage of integrating nutritional and inflammatory markers for more accurate preoperative risk stratification in rectal cancer patients.

Paliogiannis *et al*[5] demonstrated a positive connection between an increased NLR and the incidence of postoperative AL in patients who underwent elective colorectal surgery. Our study bolsters these findings, as we also noted significantly higher NLRs among patients who experienced AL after undergoing radical rectal cancer surgery. Further analysis revealed that an increased NLR was an independent risk factor for AL in our multifactorial assessments. These results suggest that the NLR could serve as a significant predictor of impending AL in the context of rectal cancer

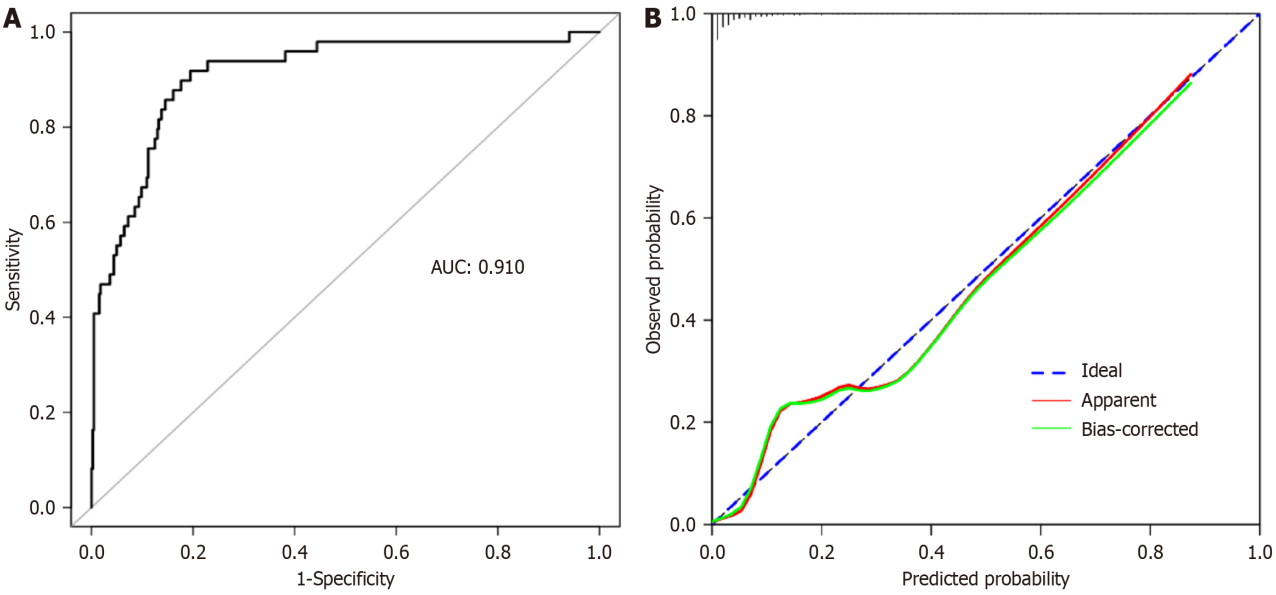


Figure 3 Receiver operating characteristic curves and calibration curves of the nomogram for predicting postoperative anastomotic leakage in patients with rectal cancer. A: Receiver operating characteristic curve of the nomogram; B: Calibration curve of the nomogram. AUC: Area under the curve. AUC: Area under the curve.

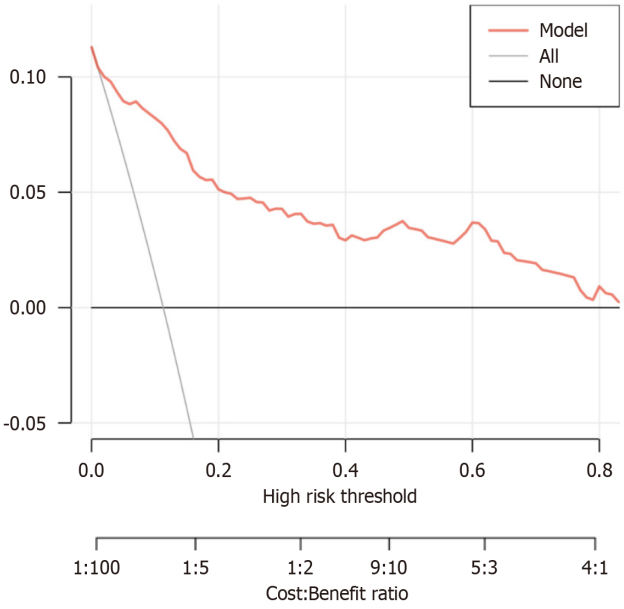


Figure 4 Decision curve analysis of the nomogram for the predicting postoperative anastomotic leakage in patients with rectal cancer.

surgery, possibly enabling clinicians to introduce prophylactic strategies in advance. Neutrophils play a dominant role in the inflammatory response, whereas LYM are involved in regulating immune homeostasis. Preoperatively, an elevated NLR usually reflects a more severe chronic inflammatory state in a patient, and an excessive inflammatory response may lead to impaired local blood flow and immunosuppression, which in turn affects the healing ability of the anastomosis. Therefore, an elevated preoperative NLR may suggest that patients are more likely to develop AL postoperatively.

Notably, the PLR, another inflammatory biomarker, is calculated as the division of the Plt count by the LYM count. Plts contribute to inflammation by secreting cytokines and chemokines that aggravate the inflammatory environment of tumors[32]. The PLR has garnered recognition as a crucial marker of inflammation. Numerous studies have linked an elevated PLR to a poor prognosis in different types of cancers, including nasopharyngeal carcinoma, prostate cancer, lung cancer, and CRC[33]. Our research revealed a statistically robust association through multifactorial analysis, demonstrating that higher PLRs are significantly correlated with an increased risk of AL postoperatively in rectal cancer patients. The inflammatory state reflected by the PLR may lead to restricted blood flow and hypoxia in the anastomotic region through enhanced Plt aggregation and altered local hemorheology, further affecting wound healing. Therefore, the preoperative PLR, as an important indicator for predicting postoperative complications, can help clinicians identify high-

risk patients preoperatively and perform timely interventions to reduce the incidence of AL.

Recent research has underscored the importance of preoperative nutritional and immune status in determining the outcomes of surgical procedures for malignant tumors[34,35]. In addition, recent studies have shown that the inflammatory response influences tumor growth by creating a favorable environment for tumor progression[36]. In this context, various serum-based parameters, such as the OPNI, NLR, MLR, PLR, and SII, have been explored as potential prognostic indicators for estimating the likelihood of perioperative AL in rectal cancer patients. After thorough data analysis, we opted for the OPNI, NLR, and PLR as key indicators due to their comprehensive reflection of the patient's nutritional state, immune status, and inflammatory response, which are crucial factors in assessing the patient's overall condition. Furthermore, the NLR, PLR, and OPNI are valued for their simplicity, speed, affordability, and minimal invasiveness, requiring only a peripheral blood sample for calculation. Numerous studies have investigated the significance of these indices in relation to postoperative complications and survival prognosis, although their value for the prediction of postoperative AL in rectal cancer patients remains underexplored.

In this study, a robust prediction model has been developed and meticulously evaluated for predicting the risk of AL after radical surgery in patients with rectal cancer. This model centers on the influential role of preoperative serum nutritional and inflammatory biomarkers in determining the likelihood of AL. Exhibiting exceptional accuracy, this model boasts an AUC of 0.910 on the ROC curve, indicating a remarkable level of sensitivity and specificity in predicting AL risk. We opted for ROC analysis, a clinically relevant and efficacious method, to evaluate our model's discriminatory potential, particularly given its proficiency in determining the performance of our predictive tool.

Although this study has several strengths, it also has several limitations, one of which is the relatively small sample size, which raises concerns about the generalizability of the findings to larger populations and potentially compromises the robustness of the statistical inferences. While the initial sample size calculation suggested a sample of 154 patients, we included 434 patients, which provides a more robust foundation for our conclusions. However, the limitation still stands as it might affect external validity when applied to broader demographics and could raise concerns about the reliability of statistical significance in different populations. As this study relied mainly on preoperative data, it failed to fully consider the impact of relevant intraoperative factors (*e.g.*, surgical approach, duration of surgery, *etc.*) on the risk of AL. Therefore, the role of these intraoperative factors has not been evaluated in this study. Future studies may include intraoperative factors in the analysis to further optimize and improve the prediction model of AL and enhance its clinical application value and accuracy. In addition, as a retrospective analysis, selection bias and information bias may exist, particularly because the data were collected from a single institution. As this study had a single-center design, the findings may not be fully applicable to other settings with different patient populations or health care environments. This could restrict the external applicability of the results. Furthermore, since the study design was retrospective in nature, we acknowledge the inherent limitations in controlling for all potential confounding factors, which could have affected the outcomes. To increase the precision and validity of the findings, future research should focus on larger-scale, multicenter, and prospective study designs, which will allow broader patient representation and more reliable conclusions. The incorporation of external validation through independent datasets and prospective cohort studies will be crucial for verifying the generalizability of our results across different institutions and geographic regions. Undoubtedly, implementing these approaches would strengthen the reliability and robustness of the findings, enabling a more extensive assessment of the suitability of the predictive model for clinical application.

CONCLUSION

We conducted a retrospective study analyzing clinical data from 434 rectal cancer patients who had undergone surgery, with a specific emphasis on preoperative serum nutritional and inflammation biomarkers, such as the OPNI, NLR, and PLR. By constructing a predictive model based on these biomarkers, we identified their potential in predicting the risk of AL. The developed model demonstrated an impressive AUC of 0.910. This study highlights the pivotal role of nutritional and inflammatory status in determining the risk of adverse surgical outcomes, contributing to a more comprehensive understanding of the factors that influence these outcomes. This finding stresses the necessity of incorporating nutritional and inflammatory evaluations into preoperative planning to optimize patient care. Such comprehensive evaluations might minimize postoperative complications, facilitate faster patient recovery, and potentially improve the long-term prognosis of rectal cancer patients.

FOOTNOTES

Author contributions: Zhang ZY wrote the original draft; Zhang ZY and Li KJ contributed to the data analysis; Zhao ZL led the quality assessments; Wang K, Sulayman S, Chen Y, Zeng XY collected the data. Chen Y and Zhao ZL contributed to the study design and supervision; Chen Y and Zhao ZL contribute equally to this study as co-corresponding authors. All authors have agreed on the manuscript to be submitted. Chen Y, a senior investigator and expert in the field of oncology, played a crucial role in the design and execution of this study. His extensive contributions to both the clinical and experimental aspects of the research were essential in shaping its objectives and ensuring its success. Dr. Chen's mentorship of junior researchers and his strategic input in data analysis and interpretation further substantiate his leadership role. Additionally, his collaborative efforts in integrating multidisciplinary approaches into the study contributed significantly to its depth and innovation. According to the authorship guidelines and based on his substantial contributions, Chen Y is appropriately listed as a co-corresponding author.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Nomogram for predicting survival after transjugular intrahepatic portosystemic shunt in portal hypertension patients with bleeding

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Abstract

BACKGROUND

Portal hypertension (PHT) is a life-threatening complication of cirrhosis, often resulting in gastrointestinal bleeding that requires transjugular intrahepatic portosystemic shunt (TIPS). While TIPS effectively reduces portal pressure, predicting long-term survival remains challenging due to the multifactorial nature of patient outcomes. Accurate survival prediction tools are lacking, and existing models often omit critical factors such as portal vein diameter. This study aimed to develop and validate a nomogram incorporating key clinical and biochemical variables to predict 1-year and 2-year survival following TIPS in PHT patients. We hypothesized that this model would provide improved risk stratification and guide clinical decisions.

AIM

To develop and validate a nomogram for predicting 1-year and 2-year survival in PHT patients post-TIPS.

METHODS

This retrospective cohort study included 848 TIPS-treated PHT patients with gastrointestinal bleeding from two tertiary hospitals (2013-2021). Mortality was the primary endpoint. Predictive variables were selected using least absolute shrinkage and selection operator regression, and a nomogram was developed with Cox regression to predict 1-year and 2-year survival. Model performance was evaluated through receiver operating characteristic curves, calibration plots,

and decision curve analysis.

RESULTS

The mean age of the included (848) patients was 53.00 years ± 12.51, where 69.58% were men. Results showed that portal vein diameter, serum creatinine, potassium, and alpha-fetoprotein were the independent predictors of post-TIPS survival. Besides, the model showed strong discriminatory ability (C-index, 0.816 in the training set; 0.827 in the validation set) and good calibration. The area under the curve for 1-year and 2-year survival in the training set were 0.890 [95% confidence interval (CI): 0.802-0.948] and 0.838 (95%CI: 0.803-0.869), respectively. The area under the curve for 1-year and 2-year survival in the validation set were 0.934 (95%CI: 0.815-0.987) and 0.864 (95%CI: 0.811-0.907), respectively.

CONCLUSION

The developed nomogram could reliably predict 1-year and 2-year survival in patients undergoing TIPS for PHT-induced gastrointestinal bleeding.

Key Words: Portal hypertension; Gastrointestinal hemorrhage; Transjugular Intrahepatic portasystemic shunt; Nomograms; Survival

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Core Tip: This study developed and validated a novel nomogram to predict 1-year and 2-year survival in patients undergoing transjugular intrahepatic portosystemic shunt for portal hypertension-induced gastrointestinal bleeding. Key prognostic factors, including portal vein diameter, serum creatinine, potassium, and alpha-fetoprotein, were identified using least absolute shrinkage and selection operator and Cox regression analyses. The model demonstrated excellent discrimination, calibration, and clinical utility across training and validation cohorts. This tool provides an innovative approach to risk stratification and personalized prognosis, offering valuable guidance for clinical decision-making and long-term management of patients receiving transjugular intrahepatic portosystemic shunt.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide. Notably, the incidence of HCC is highest in East Asia and sub-Saharan Africa, primarily due to viral hepatitis, alcohol abuse, and obesity. The global burden of HCC may increase by over 50% by 2040, mainly due to non-alcoholic steatohepatitis[1-5]. Cirrhosis-related deaths accounted for 2.4% of all global deaths in 2017[6]. Severe portal hypertension (PHT) in decompensated cirrhosis increases the risk of variceal rupture, with mortality rates of 15%-30%[7-11]. Hepatic sinusoidal endothelial dysfunction, stellate cell activation, abnormal vascular responses, and microvascular thrombosis lead to systemic circulatory expansion and exacerbate complications of PHT[12-14].

Transjugular intrahepatic portosystemic shunt (TIPS) is widely used to manage PHT and its complications by creating a shunt between the portal and hepatic veins, bypassing the fibrotic liver region. A self-expanding metal stent maintains the shunt's patency, allowing direct flow of portal venous blood into the systemic circulation, thereby reducing the pressure gradient and restoring normal blood flow[15-19]. Microvascular thrombosis exacerbates sinusoidal obstruction and liver fibrosis, increasing the risk of complications after TIPS[14]. Long-term survival after TIPS depends on liver function, the presence of HCC, and the severity of PHT[20]. Early TIPS reduces rebleeding and improves survival in high-risk cirrhotic patients, indicating that regular monitoring of portal pressure and liver function, as well as timely interventions, are essential for successful PHT treatment[21,22].

Nomograms have become popular for predicting patient prognosis in recent years by integrating clinical and biochemical variables, providing an intuitive method to estimate survival probabilities[23,24]. However, many existing models, often based on retrospective data, may lack key variables like portal vein diameter and changes in portal pressure, which are critical for long-term outcomes[10,20]. Therefore, more comprehensive and precise nomograms are needed to predict the long-term survival of patients undergoing TIPS.

This study aimed to develop and validate a nomogram for predicting 1-year and 2-year survival in patients undergoing TIPS. Key prognostic variables were identified using least absolute shrinkage and selection operator (LASSO) regression, then further analyzed with a Cox regression model[23]. The model was validated using a moderate-sized patient cohort. Therefore, the study may provide accurate risk stratification and prognosis assessment options,

optimizing treatment strategies and improving long-term survival[20,24].

MATERIALS AND METHODS

Sample size determination

A total of 848 patients were included in this study. The sample size was calculated to ensure 80% statistical power at a 0.05 significance level, based on expected effect sizes from prior studies[7,10,12]. To account for potential data loss due to incomplete medical records or patient follow-up, an additional 10% margin was incorporated into the calculation, ensuring the reliability and robustness of the results.

Ethical statement

This retrospective study was approved by the Ethics Committee of Beijing Shijitan Hospital, approval No. 2018 (1), and the Ethics Committee of the Fifth Medical Center of the General Hospital of the People's Liberation Army, approval No. KY-2023-12-83-1. Since this study was based on patients' routine treatment procedures without additional interventions or harm, informed consent was waived in the clinical setting. The study adhered to the Declaration of Helsinki and relevant ethical guidelines, ensuring patient privacy and compliance with scientific and ethical standards.

Patients

This study was conducted at the Liver Disease Minimally Invasive Treatment Center in Beijing Shijitan Hospital, Capital Medical University, and the Center for Diagnosis and Treatment of Hepatic Vascular Diseases in the Fifth Medical Center of Chinese PLA General Hospital. Only patients who underwent TIPS for PHT-related gastrointestinal bleeding between January 2013 and June 2021 and with follow-up completed by June 2023 were included in the study. Patients with recurrent esophageal variceal bleeding, refractory ascites, Budd-Chiari syndrome, or Child-Turcotte-Pugh B or C classification without severe hepatic encephalopathy underwent TIPS. Contraindications included severe liver failure and uncontrolled hepatic encephalopathy[22,25]. Finally, 107 of 955 screened patients were excluded. Exclusion criteria included: Patients with non-HCC malignancies (n = 17), missing key clinical data (n = 18), severe cardiac, renal dysfunction (n = 34), and those undergoing repeat TIPS (n = 26) or liver transplantation postoperatively (n = 12). The remaining 848 patients were randomly assigned to a training set (n = 593) and a validation set (n = 255).

Surgical procedure

The TIPS procedures were performed by experienced physicians under fluoroscopic guidance *via* a transjugular approach. First, a catheter was inserted into the inferior vena cava and hepatic vein, followed by venography to define the anatomical characteristics and measure pressures. The portal vein was then accessed by puncturing the hepatic segment of the inferior vena cava or the hepatic vein, and venography was performed to measure portal pressure. A stent was placed between the portal vein and the inferior vena cava after dilating the liver parenchymal tract. The portal pressure was measured, and the pressure gradient between the portal vein and inferior vena cava was calculated[12,26,27].

Data collection

The baseline demographic information, clinical parameters before and after surgery, imaging findings, and laboratory results were collected from the hospital's electronic medical records for quality control. Key variables included portal vein diameter, creatinine, potassium, and alpha-fetoprotein (AFP)[28]. Portal vein diameter was measured through imaging, while creatinine, potassium, and AFP levels were determined *via* blood tests. The measurements were taken within one week before TIPS procedure. Data collection and analysis were conducted by independent reviewers blinded to patient group assignments following standardized procedures to maintain accuracy and consistency, thus ensuring unbiased predictions and reducing potential bias.

Follow-up

The patients were followed for two years to track survival and postoperative complications. Follow-up data were collected through outpatient visits, telephone interviews, and electronic medical record system. The primary endpoint was all-cause mortality, defined as death from any cause during the follow-up period.

Statistical analysis

R software (version 4.4.1; https://www.R-project.org) and MedCalc software (version 22.001; https://www.medcalc.org) were used for statistical analyses. There were no missing data in this study. Quantitative data were presented as median (interquartile range), and comparisons between groups were performed using the independent sample t-test or Mann-Whitney U test, depending on data distribution. Categorical data were expressed as frequencies and percentages, and comparisons were made using the χ^2 test or Fisher's exact test. Variables, such as portal vein diameter, creatinine, potassium, and AFP, were log-transformed before analysis to improve normality and model robustness. Key survival-related variables were identified using LASSO regression. A nomogram predicting 1-year and 2-year survival probabilities was built using Cox regression analysis. Model performance was evaluated using receiver operating characteristic curves and area under the curve (AUC), with calibration assessed by the Hosmer-Lemeshow test. Net benefit at various thresholds was assessed using decision curve analysis to confirm the model's applicability across clinical decision-making scenarios. Survival between high-risk and low-risk groups was compared using Kaplan-Meier survival analysis. Patients

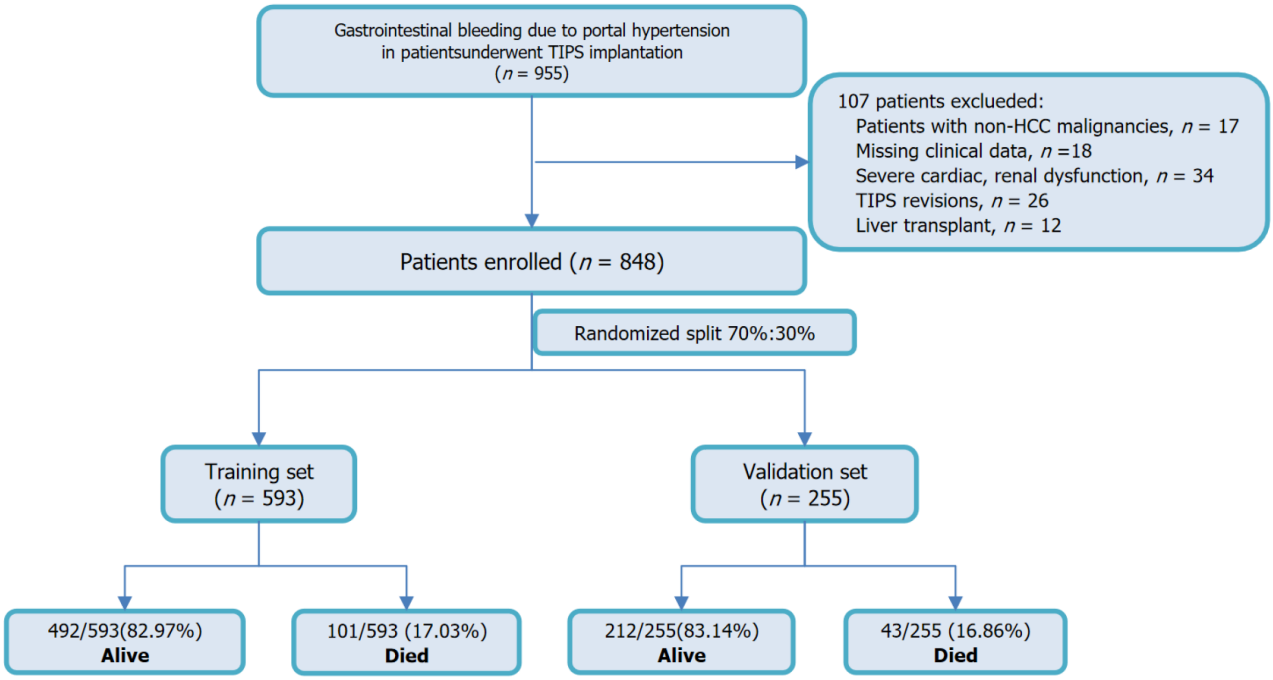


Figure 1 Flowchart of this study. TIPS: Transjugular intrahepatic portosystemic shunt; HCC: Hepatocellular carcinoma.

lost to follow-up were censored at their last recorded follow-up date in survival analysis. A two-sided *P* value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 848 patients with PHT-induced gastrointestinal bleeding who underwent TIPS were included in the study. The patients were randomly assigned to the training set (593 patients) and validation set (255 patients) in a 7:3 ratio. The mean follow-up duration was 20.85 ± 6.82 months. During follow-up, 59 patients (6.96%) were lost to follow-up due to uncontactable status or withdrawal from the study. By the end of the first year, 80 patients (9.43%) had died, and by the end of the second year, the total number of deaths had reached 144 (16.98%). In the training set, 101 patients died, while 43 deaths occurred in the validation set (survival rates: 82.97% and 83.14%, respectively; *P* value = 0.90, Figure 1). The primary causes of death were liver failure, HCC, hepatic encephalopathy, and rebleeding.

Compared with survivors, non-survivors had significantly higher preoperative portal vein pressure, pressure gradient, and right hepatic vein wedge pressure, with reduced portal vein diameter. Furthermore, creatinine and AFP levels of non-survivors were elevated, while potassium levels were reduced (Table 1). In both the training and validation cohorts, non-survivors exhibited distinct baseline characteristics compared to survivors. In the training cohort, they had a higher pre-TIPS portal pressure gradient (*P* value = 0.031) and a smaller portal vein diameter (*P* value < 0.001), along with elevated serum creatinine (*P* value < 0.001), lower potassium (*P* value < 0.001), and significantly higher AFP levels (*P* value < 0.001). Similarly, in the validation cohort, non-survivors had higher pre-TIPS portal venous pressure (*P* value = 0.034), smaller portal vein diameter (*P* value < 0.001), increased serum creatinine (*P* value < 0.001), lower potassium (*P* value = 0.022), and decreased albumin levels (*P* value = 0.012). Additionally, AFP (*P* value < 0.001) and cancer antigen 125 (*P* value = 0.049) were significantly elevated in non-survivors (Tables 2 and 3). Notably, the baseline characteristics, including age, gender, Child-Turcotte-Pugh classification, and portal vein pressure, were not significantly different between the training and validation sets. Biochemical indices were also consistent in both sets (Table 4).

Identification of predictive factors

LASSO regression was first applied to the training set using the glmnet package (α = 1, Nlambda = 100) to select key prognostic variables while minimizing overfitting. 10-fold cross-validation determined the optimal lambda (λ = 0.028), yielding four significant predictors: Portal vein diameter (β = -1.256), creatinine (β = 0.613), potassium (β = -2.316), and AFP (β = 0.261). These LASSO-identified variables were further subjected to univariate Cox regression, confirming their significant association with survival (*P* value < 0.05). Multivariate Cox analysis validated their independent prognostic value: Portal vein diameter [hazard ratio (HR) = 0.195, *P* value < 0.001] and potassium (HR = 0.030, *P* value < 0.001) were protective factors, whereas creatinine (HR = 1.947, *P* value = 0.019) and AFP (HR = 1.455, *P* value < 0.001) were associated with increased mortality risk (Figure 2A, Table 5).

Table 1 Baseline demographic and clinical characteristics of patients stratified by survival status, *n* (%)

Characteristic	Overall (*n* = 848)	Survivors (*n* = 704)	Non-survivors (*n* = 144)	*P* value
Age (year)	53.00 (45.00-61.00)	52.00 (45.00-61.00)	55.00 (46.00-63.00)	0.094
Sex				
Male	590 (69.58)	492 (69.89)	98 (68.06)	0.664
Female	258 (30.42)	212 (30.11)	46 (31.94)	-
Pre-TIPS Child Pugh class				
A	417 (49.17)	349 (49.57)	68 (47.22)	0.391
B	372 (43.87)	303 (43.04)	69 (47.92)	-
C	59 (6.96)	52 (7.39)	7 (4.86)	-
Etiology				
Alcohol	97 (11.44)	75 (10.65)	22 (15.28)	0.488
Autoimmune liver disease	46 (5.42)	40 (5.68)	6 (4.17)	-
Cryptogenic	252 (29.72)	207 (29.40)	45 (31.25)	-
Drug-induced liver injury	18 (2.12)	16 (2.27)	2 (1.39)	-
Hepatitis B virus	391 (46.11)	331 (47.02)	60 (41.67)	-
Hepatitis C virus	44 (5.19)	35 (4.97)	9 (6.25)	-
Pre-TIPS portal venous pressure (mmHg)	33.04 (29.00-37.55)	33.00 (29.00-37.00)	35.00 (31.00-38.48)	0.005[b]
Post-TIPS portal venous pressure (mmHg)	22.00 (18.00-26.00)	22.00 (18.00-26.00)	21.00 (17.00-25.13)	0.157
Pre-TIPS inferior vena cava pressure (mmHg)	8.00 (6.00-10.00)	8.00 (6.00-10.00)	8.00 (6.00-10.00)	0.861
Post-TIPS inferior vena cava pressure (mmHg)	9.00 (8.00-12.00)	9.00 (8.00-11.00)	10.00 (7.00-12.00)	0.523
Pre-TIPS portal pressure gradient (mmHg)	25.47 (21.03-29.79)	25.00 (21.00-29.05)	26.90 (23.00-30.43)	0.008[b]
Post-TIPS porta pressure gradient (mmHg)	11.72 (8.00-15.78)	12.00 (8.00-15.78)	11.00 (6.71-15.53)	0.096
Portal vein diameter (mm)	12.00 (10.20-15.82)	13.00 (11.00-16.00)	10.95 (8.93-13.00)	< 0.001[b]
Right hepatic vein wedge pressure (mmHg)	27.00 (21.00-32.00)	27.00 (21.00-32.00)	27.00 (23.28-35.00)	0.039[a]
Right hepatic vein free pressure (mmHg)	10.75 (9.00-12.00)	10.75 (8.26-12.00)	10.75 (9.74-12.00)	0.426
Pre-TIPS right atrial pressure (mmHg)	6.13 (5.00-6.13)	6.13 (5.00-6.13)	6.13 (5.00-6.13)	0.398
Pre-TIPS Child-Pugh score	7.00 (6.00-8.00)	7.00 (6.00-8.00)	7.00 (6.00-8.00)	0.756
Pre-TIPS MELD score	59.96 (56.61-63.00)	59.98 (56.57-62.94)	59.80 (56.97-63.96)	0.472
Total bilirubin (μmol/L)	22.65 (15.90-34.80)	22.70 (16.07-34.50)	22.50 (15.70-35.47)	0.841
Direct bilirubin (μmol/L)	9.90 (6.70-15.93)	10.00 (6.70-15.70)	9.60 (6.30-17.53)	0.899
Indirect bilirubin (μmol/L)	12.80 (8.98-19.62)	12.85 (8.98-19.70)	12.60 (9.12-18.58)	0.747
Creatinine (μmol/L)	62.00 (52.00-74.00)	60.50 (51.00-72.00)	70.00 (60.00-87.00)	< 0.001[b]
Alanine aminotransferase (U/L)	20.00 (14.00-29.00)	19.00 (14.00-28.00)	21.00 (15.00-30.00)	0.326
Aspartate aminotransferase (U/L)	28.00 (21.00-38.00)	27.00 (21.00-37.00)	29.50 (21.00-43.00)	0.107
Kalium (mmol/L)	3.94 (3.62-4.22)	3.96 (3.68-4.23)	3.79 (3.28-4.07)	< 0.001[b]
Natrium (mmol/L)	140.00 (138.00-142.00)	140.00 (138.00-142.00)	140.00 (138.00-142.00)	0.844
Chlorine (mmol/L)	107.00 (104.00-109.00)	107.00 (104.00-109.00)	107.00 (105.00-109.25)	0.356
Alkaline phosphatase (U/L)	88.00 (66.00-123.00)	87.00 (66.00-122.00)	89.00 (68.75-129.25)	0.343
Glutamyl transferase (U/L)	38.00 (20.00-73.00)	39.00 (20.00-71.00)	34.50 (18.75-89.25)	0.875
Serum urea nitrogen (mmol/L)	4.91 (3.99-6.41)	4.88 (3.96-6.38)	5.07 (4.13-6.48)	0.369
Total protein (g/L)	66.10 (61.71-70.40)	66.10 (61.79-70.52)	66.00 (61.40-70.00)	0.885
Albumin (g/L)	35.73 (32.10-39.12)	35.73 (32.10-39.22)	35.75 (32.42-38.75)	0.862

International normalized ratio	1.27 (1.15-1.44)	1.28 (1.16-1.43)	1.25 (1.14-1.45)	0.467
Activated partial thromboplastin time (second)	33.40 (31.00-36.83)	33.35 (30.97-36.80)	33.75 (31.27-37.20)	0.463
Prothrombin time (second)	14.00 (12.70-15.72)	14.20 (12.70-15.70)	13.80 (12.57-15.85)	0.497
Prothrombin time activity (%)	66.00 (56.00-77.00)	66.00 (57.00-77.00)	69.00 (55.00-76.25)	0.913
Fibrinogen (g/L)	1.99 (1.57-2.50)	2.00 (1.57-2.46)	1.88 (1.55-2.62)	0.904
Blood ammonia (μmol/L)	42.64 (32.40-59.50)	42.80 (32.50-58.92)	41.35 (31.95-60.73)	0.755
White blood cell count ($\times 10^9$/L)	2.83 (1.90-4.19)	2.78 (1.90-4.11)	3.18 (1.89-4.46)	0.188
Hemoglobin ($\times 10^{12}$/L)	86.50 (74.00-104.00)	87.00 (74.00-103.25)	85.00 (75.00-107.25)	0.884
Platelet count ($\times 10^9$/L)	76.00 (50.00-121.00)	77.00 (50.00-121.25)	74.50 (54.00-115.25)	0.888
Alpha fetoprotein (ng/mL)	220.56 (2.85-423.31)	14.85 (2.52-365.37)	536.56 (365.37-1290.49)	< 0.001[b]
Carcinoembryonic antigen (ng/mL)	2.44 (1.62-3.61)	2.42 (1.62-3.58)	2.48 (1.60-3.92)	0.711
Carbohydrate antigen 125 (U/mL)	125.24 (36.20-233.29)	120.40 (35.90-222.78)	151.99 (39.64-281.48)	0.109
Cancer antigen 15-3 (U/mL)	10.30 (7.50-14.20)	10.30 (7.50-14.20)	10.50 (7.47-14.12)	0.889
Glycosylated chain antigen CA199 (U/mL)	10.94 (4.43-15.26)	10.57 (4.28-15.26)	12.46 (4.69-15.26)	0.265

[a]$P < 0.05$.
[b]$P < 0.01$.
MELD: Model for end-stage liver disease; TIPS: Transjugular intrahepatic portosystemic shunt; CA199: Carbohydrate antigen 199.

Table 2 Baseline demographic and clinical characteristics of patients in the training set stratified by survival status, *n* (%)

Characteristic	Overall (*n* = 593)	Survivors (*n* = 492)	Non-survivors (*n* = 101)	*P* value
Age (year)	53.00 (46.00-61.00)	53.00 (46.00-60.00)	56.00 (48.00-63.00)	0.109
Sex	-	-	-	0.459
Male	406 (68.47)	340 (69.11)	66 (65.35)	-
Female	187 (31.53)	152 (30.89)	35 (34.65)	-
Pre-TIPS Child-Turcotte-Pugh class	-	-	-	0.35
A	292 (49.24)	243 (49.39)	49 (48.51)	-
B	259 (43.68)	211 (42.89)	48 (47.52)	-
C	42 (7.08)	38 (7.72)	4 (3.96)	-
Etiology	-	-	-	0.818
Alcohol	61 (10.29)	48 (9.76)	13 (12.87)	-
Autoimmune liver disease	37 (6.24)	31 (6.30)	6 (5.94)	-
Cryptogenic	180 (30.35)	146 (29.67)	34 (33.66)	-
Drug-induced liver injury	15 (2.53)	13 (2.64)	2 (1.98)	-
Hepatitis B virus	267 (45.03)	227 (46.14)	40 (39.60)	-
Hepatitis C virus	33 (5.56)	27 (5.49)	6 (5.94)	-
Pre-TIPS portal venous pressure (mmHg)	33.80 (29.29-37.55)	33.02 (29.00-37.00)	34.17 (31.00-37.55)	0.057
Post-TIPS portal venous pressure (mmHg)	21.87(15.96-27.78)	21.98 (16.05-27.91)	21.32 (15.54-27.10)	0.305
Pre-TIPS inferior vena cava pressure (mmHg)	8.00 (6.00-10.00)	8.00 (6.00-10.00)	7.00 (5.00-10.00)	0.482
Post-TIPS inferior vena cava pressure (mmHg)	9.00 (8.00-11.00)	9.00 (8.00-11.00)	9.00 (7.00-12.00)	0.733
Pre-TIPS portal pressure gradient (mmHg)	25.30 (21.00-30.00)	25.00 (21.00-30.00)	26.80 (23.00-30.00)	0.031[a]
Post-TIPS porta pressure gradient (mmHg)	11.90 (8.00-15.91)	12.00 (8.00-15.81)	11.00 (7.00-16.00)	0.336
Portal vein diameter (mm)	12.00 (10.30-15.80)	13.00 (11.00-16.00)	11.00 (9.00-14.00)	< 0.001[b]

Right hepatic vein wedge pressure (mmHg)	27.00 (21.00-32.00)	27.00 (21.00-32.00)	27.00 (22.00-32.29)	0.179
Right hepatic vein free pressure (mmHg)	10.75 (9.00-12.00)	10.75 (9.00-12.00)	10.75 (10.00-12.00)	0.543
Pre-TIPS right atrial pressure (mmHg)	6.13 (5.00-6.13)	6.13 (5.00-6.13)	6.13 (5.00-6.13)	0.98
Pre-TIPS Child-Turcotte-Pugh score	7.00 (5.00-8.00)	7.00 (5.00-8.00)	7.00 (6.00-8.00)	0.888
Pre-TIPS MELD score	60.10 (56.68-63.25)	60.07 (56.55-63.15)	60.27 (57.39-63.35)	0.754
Total bilirubin (μmol/L)	22.70 (16.00-35.20)	22.70 (15.88-35.53)	22.90 (16.05-33.90)	0.953
Direct bilirubin (μmol/L)	9.80 (6.50-16.30)	9.85 (6.57-16.45)	9.30 (6.30-15.60)	0.62
Indirect bilirubin (μmol/L)	13.20 (9.00-19.40)	13.30 (8.82-19.70)	12.80 (9.67-17.60)	0.915
Creatinine (μmol/L)	62.00 (52.00-74.00)	61.00 (51.00-72.00)	69.00 (59.00-87.00)	< 0.001[b]
Alanine aminotransferase (U/L)	19.00 (14.00-27.69)	19.00 (14.00-27.00)	20.00 (15.00-30.00)	0.598
Aspartate aminotransferase (U/L)	28.00 (21.00-37.00)	27.50 (21.00-37.00)	29.00 (21.00-39.99)	0.253
Kalium (mmol/L)	3.94 (3.61-4.24)	3.97 (3.68-4.25)	3.77 (3.22-4.08)	< 0.001[b]
Natrium (mmol/L)	140.00 (138.00-142.00)	140.00 (138.00-142.00)	140.00 (139.00-142.00)	0.979
Chlorine (mmol/L)	107.00 (104.00-109.00)	107.00 (104.00-109.00)	107.00 (105.00-109.00)	0.761
Alkaline phosphatase (U/L)	86.00 (66.00-121.00)	85.00 (66.00-121.00)	88.00 (69.00-119.00)	0.587
Glutamyl transferase (U/L)	37.00 (20.00-71.00)	38.00 (20.75-71.00)	35.00 (18.00-81.00)	0.526
Serum urea nitrogen (mmol/L)	4.97 (4.04-6.44)	4.94 (4.02-6.44)	5.09 (4.16-6.39)	0.674
Total protein (g/L)	66.03 (61.30-70.00)	66.09 (61.30-70.30)	65.75 (61.27-69.50)	0.863
Albumin (g/L)	35.80 (32.30-39.30)	35.75 (32.10-39.30)	36.20 (33.40-39.80)	0.285
International normalized ratio	1.27 (1.15-1.42)	1.27 (1.15-1.41)	1.26 (1.14-1.44)	0.727
Activated partial thromboplastin time (second)	33.50 (30.90-37.10)	33.50 (30.90-37.10)	33.50 (31.00-37.20)	0.939
Prothrombin time (second)	13.90 (12.70-15.50)	13.90 (12.70-15.52)	13.90 (12.50-15.50)	0.794
Prothrombin time activity (%)	67.00 (57.00-77.00)	67.00 (57.00-77.00)	69.00 (56.00-76.00)	0.943
Fibrinogen (g/L)	1.98 (1.56-2.48)	2.00 (1.57-2.45)	1.82 (1.55-2.60)	0.639
Blood ammonia (μmol/L)	42.30 (32.20-58.65)	42.55 (32.68-58.00)	39.40 (30.00-59.10)	0.264
White blood cell count (× 10^9/L)	2.88 (1.90-4.14)	2.83 (1.92-4.10)	3.19 (1.84-4.38)	0.608
Hemoglobin (× 10^{12}/L)	87.00 (74.00-104.00)	86.50 (74.00-103.00)	87.00 (76.00-111.00)	0.181
Platelet count (× 10^9/L)	76.00 (50.00-116.00)	77.00 (49.75-117.25)	75.00 (51.00-108.00)	0.927
Alpha fetoprotein (ng/mL)	233.19 (2.88-413.82)	23.04 (2.57-365.37)	575.44 (365.37-1328.95)	< 0.001[b]
Carcinoembryonic antigen (ng/mL)	2.40 (1.63-3.54)	2.40 (1.63-3.54)	2.46 (1.57-3.59)	0.829
Carbohydrate antigen 125 (U/mL)	137.25 (40.10-242.69)	136.20 (40.05-232.68)	145.69 (40.20-284.55)	0.513
Cancer antigen 15-3 (U/mL)	10.30 (7.50-14.10)	10.30 (7.50-14.10)	9.90 (7.40-13.90)	0.71
Glycosylated chain antigen CA199 (U/mL)	11.47 (4.81-15.26)	11.71 (4.83-15.26)	9.50 (4.70-15.26)	0.913

[a]$P < 0.05$.
[b]$P < 0.01$.
MELD: Model for end-stage liver disease; TIPS: Transjugular intrahepatic portosystemic shunt; CA199: Carbohydrate antigen 199.

Table 3 Baseline demographic and clinical characteristics of patients in the validation set stratified by survival status, *n* (%)

Characteristic	Overall (*n* = 255)	Survivors (*n* = 212)	Non-survivors (*n* = 43)	*P* value
Age (year)	51.00(64.44-37.56)	50.68(37.02-64.34)	52.58(40.25-64.91)	0.4
Sex	-	-	-	0.717
Male	184 (72.16)	152 (71.70)	32 (74.42)	-

Female	71 (27.84)	60 (28.30)	11 (25.58)	-
Pre-TIPS Child-Turcotte-Pugh class	-	-	-	0.782
A	125 (49.02)	106 (50.00)	19 (44.19)	-
B	113 (44.31)	92 (43.40)	21 (48.84)	-
C	17 (6.67)	14 (6.60)	3 (6.98)	-
Etiology	-	-	-	0.397
Alcohol	36 (14.12)	27 (12.74)	9 (20.93)	-
Autoimmune liver disease	9 (3.53)	9 (4.25)	0 (0.00)	-
Cryptogenic	72 (28.24)	61 (28.77)	11 (25.58)	-
Drug-induced liver injury	3 (1.18)	3 (1.42)	0 (0.00)	-
Hepatitis B virus	124 (48.63)	104 (49.06)	20 (46.51)	-
Hepatitis C virus	11 (4.31)	8 (3.77)	3 (6.98)	-
Pre-TIPS portal venous pressure (mmHg)	33.04 (29.00-38.00)	33.00 (28.88-37.00)	36.00 (30.52-39.40)	0.034[a]
Post-TIPS portal venous pressure (mmHg)	21.83 (15.27-28.39)	21.93(15.54-28.32)	21.31(13.90-28.72)	0.57
Pre-TIPS inferior vena cava pressure (mmHg)	8.00 (6.00-10.00)	8.00 (6.00-10.00)	9.00 (6.00-10.00)	0.156
Post-TIPS inferior vena cava pressure (mmHg)	10.00 (8.00-12.00)	9.00 (7.00-11.25)	11.00 (8.00-13.26)	0.087
Pre-TIPS portal pressure gradient (mmHg)	26.00 (21.66-29.00)	25.00 (21.23-29.00)	27.05 (23.00-31.00)	0.097
Post-TIPS porta pressure gradient (mmHg)	11.02 (7.00-15.53)	11.65 (7.88-15.60)	10.78 (5.00-15.00)	0.108
Portal vein diameter (mm)	12.70 (10.20-15.85)	13.00 (11.00-16.07)	10.20 (8.61-12.20)	< 0.001[b]
Right hepatic vein wedge pressure (mmHg)	27.00 (23.00-31.77)	27.00 (22.00-31.00)	27.00 (26.00-35.15)	0.086
Right hepatic vein free pressure (mmHg)	10.75 (8.00-12.00)	10.75 (8.00-12.00)	10.75 (9.00-13.00)	0.571
Pre-TIPS right atrial pressure (mmHg)	6.13 (4.25-7.00)	6.13 (4.00-6.82)	6.13 (6.00-8.00)	0.133
Pre-TIPS Child-Turcotte-Pugh score	7.00 (6.00-8.00)	6.50 (6.00-8.00)	7.00 (6.00-8.00)	0.419
Pre-TIPS MELD score	59.59 (56.59-62.66)	59.63 (56.60-62.49)	58.73 (56.61-64.72)	0.452
Total bilirubin (μmol/L)	22.10 (15.90-34.30)	22.30 (16.40-32.92)	21.80 (14.85-38.40)	0.813
Direct bilirubin (μmol/L)	10.50 (6.95-15.30)	10.45 (7.20-14.68)	11.30 (6.25-18.50)	0.574
Indirect bilirubin (μmol/L)	12.20 (8.95-19.82)	12.25 (9.28-19.65)	11.70 (7.46-20.25)	0.599
Creatinine (μmol/L)	62.00 (51.50-73.00)	60.00 (50.00-70.00)	72.00 (63.50-86.50)	< 0.001[b]
Alanine aminotransferase (U/L)	21.00 (13.50-29.00)	19.50 (13.00-29.00)	21.00 (15.00-31.00)	0.371
Aspartate aminotransferase (U/L)	27.00 (21.00-41.50)	27.00 (21.00-39.00)	30.00 (22.00-46.50)	0.244
Kalium (mmol/L)	3.91(3.45-4.37)	3.94(3.50-4.38)	3.77 (3.27-4.27)	0.022[a]
Natrium (mmol/L)	140.00(138.00-142.00)	140.00(138.00-142.00)	140.00 (138.00-142.00)	0.681
Chlorine (mmol/L)	107.00(104.00-109.00)	107.00(104.00-109.00)	107.00 (103.00-111.00)	0.252
Alkaline phosphatase (U/L)	90.00 (67.00-136.50)	90.00(66.75-127.39)	94.00 (68.50-164.63)	0.35
Glutamyl transferase (U/L)	41.00 (19.00-78.50)	41.00 (18.00-74.00)	34.00 (25.00-108.00)	0.225
Serum urea nitrogen (mmol/L)	4.78 (3.90-6.29)	4.79 (3.88-6.22)	4.74 (4.06-7.54)	0.352
Total protein (g/L)	66.47 (62.41-71.65)	66.33 (62.48-71.50)	66.51 (61.85-72.45)	0.964
Albumin (g/L)	35.51(30.44-40.58)	35.87 (30.92-40.82)	33.74 (28.44-39.04)	0.012[a]
International normalized Ratio	1.30 (1.16-1.44)	1.31 (1.17-1.44)	1.24 (1.14-1.52)	0.505
Activated partial thromboplastin time (s)	33.20 (31.20-36.00)	33.10 (31.08-35.70)	34.70 (31.40-37.20)	0.125
Prothrombin time (s)	14.40 (12.80-16.00)	14.40 (12.97-16.00)	13.70 (12.60-16.70)	0.472
Prothrombin time activity (%)	65.39 (49.85-80.93)	65.45 (50.32-80.58)	65.05 (47.44-82.66)	0.876
Fibrinogen (g/L)	2.01 (1.62-2.54)	2.01 (1.61-2.53)	2.22 (1.69-2.79)	0.343

Blood ammonia (μmol/L)	43.40 (32.95-62.85)	43.25 (32.00-60.83)	44.30 (35.20-64.60)	0.264
White blood cell count (× 10^9/L)	2.72 (1.86-4.23)	2.69 (1.82-4.16)	3.02 (2.23-4.79)	0.084
Hemoglobin (× 10^{12}/L)	86.00 (75.00-104.00)	88.00 (75.75-106.25)	81.00 (71.00-95.50)	0.069
Platelet count (× 10^9/L)	76.00 (52.00-123.50)	79.50 (51.00-124.25)	73.00 (59.00-123.50)	0.897
Alpha fetoprotein (ng/mL)	156.85 (2.66-428.81)	7.46 (2.38-365.37)	408.14 (307.14-1191.07)	< 0.001[b]
Carcinoembryonic antigen (ng/mL)	2.64 (1.60-3.75)	2.65 (1.56-3.66)	2.63 (1.77-4.48)	0.716
Carbohydrate antigen 125 (U/mL)	100.70 (33.20-204.23)	91.51 (30.60-178.03)	166.87 (41.43-270.85)	0.049[a]
Cancer antigen 15-3 (U/mL)	10.40 (7.10-14.65)	10.25 (7.00-14.62)	10.80 (7.95-14.85)	0.829
Glycosylated chain antigen CA199 (U/mL)	9.26 (4.07-15.26)	9.01 (4.01-15.26)	15.26 (5.02-15.26)	0.068

[a]$P < 0.05$.
[b]$P < 0.01$.
MELD: Model for end-stage liver disease; TIPS: Transjugular intrahepatic portosystemic shunt; CA199: Carbohydrate antigen 199.

Development of an individualized prediction model
In this study, the predictive model was constructed exclusively using the training set and subsequently validated in an independent validation set. The developed nomogram is shown in Figure 2B. The nomogram included potassium, creatinine, AFP, and portal vein diameter and estimated patient survival probability by summing the scores of these variables. Cox regression analysis indicated that potassium (β = -3.508, *P* value < 0.001) and portal vein diameter (β = -1.635, *P* value < 0.001) were protective factors, while AFP (β = 0.375, *P* value < 0.001) and creatinine (β = 0.667, *P* value = 0.019) were associated with worse prognosis. For instance, a post-TIPS patient with a portal vein diameter of 12 mm, creatinine of 50 μmol/L, potassium of 4.0 mmol/L, and AFP of 500 ng/mL had an estimated 1-year and 2-year mortality rates of 9.5% and 19.5%, respectively (Figure 2C).

Discrimination
The discrimination ability of the model was evaluated based on several metrics, such as the likelihood ratio χ^2 test, C-index, and AUC. The likelihood ratio χ^2 value was 146.17 (*P* value < 0.01), yielding a C-index of 0.816 [95% confidence interval (CI): 0.777-0.855] in the training set and 0.827 (95%CI: 0.771-0.883) in the validation set. The AUC for 1-year and 2-year survival in the training set were 0.890 (95%CI: 0.802-0.948) and 0.838 (95%CI: 0.803-0.869), respectively. The AUC for 1-year and 2-year survival in the validation set were 0.934 (95%CI: 0.815-0.987) and 0.864 (95%CI: 0.811-0.907), respectively. These results demonstrate strong discrimination ability at different time points (Figure 3).

Calibration of the predictive model
The calibration of the nomogram model in the training and validation sets is shown in Figure 4. The calibration curves in both sets showed strong alignment between predicted and observed survival rates. Similarly, Hosmer-Lemeshow test results indicated good calibration in both sets, with *P* value of 1.

Clinical use
Decision curve analysis of the nomogram in both the training and validation sets, assessing net benefit across different risk thresholds, is shown in Figure 5. The optimal probability ranges for 1-year and 2-year survival prediction in the training set were 2%-49%, and 3%-99%, respectively: And 2%-56% and 3%-97%, respectively, in the validation set. The nomogram yielded the greatest net benefit within these ranges.

Risk stratification
The patients in the training and validation sets were stratified into high-risk and low-risk groups based on the optimal cut-off value of the risk score (1.625). Kaplan-Meier analysis showed that the high-risk groups had significantly lower survival rates than the low-risk groups (*P* value < 0.0001, Figure 6).

DISCUSSION
In this study, a nomogram was developed and validated for the prediction of 1-year and 2-year survival in patients with PHT-induced gastrointestinal bleeding who underwent TIPS. Portal vein diameter, creatinine, potassium, and AFP were identified as key factors influencing long-term survival. Besides, these variables demonstrated significant independent prognostic value. The nomogram effectively predicted postoperative survival, showing strong discrimination ability and good calibration in the training and validation sets. Kaplan-Meier analysis further confirmed that the survival was significantly different between the high-risk and low-risk groups. PHT management strategies influence the model application and long-term prognosis. Notably, TIPS should be conducted cautiously for patients with both HCC and

Table 4 Baseline demographic and clinical characteristics of the training and validation cohorts, *n* (%)

Characteristic	Overall (*n* = 848)	Training cohort (*n* = 593)	Validation cohort (*n* = 255)	*P* value
Age (year)	53.00 (45.00-61.00)	53.00 (46.00-61.00)	51.00 (42.00-62.00)	0.078
Sex				
Male	590 (69.58)	406 (68.47)	184 (72.16)	0.284
Female	258 (30.42)	187 (31.53)	71 (27.84)	-
Pre-TIPS Child Pugh class				
A	417 (49.17)	292 (49.24)	125 (49.02)	0.969
B	372 (43.87)	259 (43.68)	113 (44.31)	-
C	59 (6.96)	42 (7.08)	17 (6.67)	-
Etiology				
Alcohol	97 (11.44)	61 (10.29)	36 (14.12)	0.183
Autoimmune liver disease	46 (5.42)	37 (6.24)	9 (3.53)	-
Cryptogenic	252 (29.72)	180 (30.35)	72 (28.24)	-
Drug-induced liver injury	18 (2.12)	15 (2.53)	3 (1.18)	-
Hepatitis B virus	391 (46.11)	267 (45.03)	124 (48.63)	-
Hepatitis C virus	44 (5.19)	33 (5.56)	11 (4.31)	-
Pre-TIPS portal venous pressure (mmHg)	33.04 (29.00-37.55)	33.80 (29.29-37.55)	33.04 (29.00-38.00)	0.632
Post-TIPS portal venous pressure (mmHg)	22.00 (18.00-26.00)	22.00 (18.00-26.00)	22.00 (17.27-26.00)	0.774
Pre-TIPS inferior vena cava pressure (mmHg)	8.00 (6.00-10.00)	8.00 (6.00-10.00)	8.00 (6.00-10.00)	0.998
Post-TIPS inferior vena cava pressure (mmHg)	9.00 (8.00-12.00)	9.00 (8.00-11.00)	10.00 (8.00-12.00)	0.212
Pre-TIPS portal pressure gradient (mmHg)	25.47 (21.03-29.79)	25.30 (21.00-30.00)	26.00 (21.66-29.00)	0.991
Post-TIPS porta pressure gradient (mmHg)	11.72 (8.00-15.78)	11.90 (8.00-15.91)	11.02 (7.00-15.53)	0.311
Portal vein diameter (mm)	12.00 (10.20-15.82)	12.00 (10.30-15.80)	12.70 (10.20-15.85)	0.683
Right hepatic vein wedge pressure (mmHg)	27.00 (21.00-32.00)	27.00 (21.00-32.00)	27.00 (23.00-31.77)	0.637
Right hepatic vein free pressure (mmHg)	10.75 (9.00-12.00)	10.75 (9.00-12.00)	10.75 (8.00-12.00)	0.706
Pre-TIPS right atrial pressure (mmHg)	6.13 (5.00-6.13)	6.13 (5.00-6.13)	6.13 (4.25-7.00)	0.911
Pre-TIPS Child-Pugh score	7.00 (6.00-8.00)	7.00 (5.00-8.00)	7.00 (6.00-8.00)	0.600
Pre-TIPS MELD score	59.96 (56.61-63.00)	60.10 (56.68-63.25)	59.59 (56.59-62.66)	0.376
Total bilirubin (μmol/L)	22.65 (15.90-34.80)	22.70 (16.00-35.20)	22.10 (15.90-34.30)	0.882
Direct bilirubin (μmol/L)	9.90 (6.70-15.93)	9.80 (6.50-16.30)	10.50 (6.95-15.30)	0.424
Indirect bilirubin (μmol/L)	12.80 (8.98-19.62)	13.20 (9.00-19.40)	12.20 (8.95-19.82)	0.371
Creatinine (μmol/L)	62.00 (52.00-74.00)	62.00 (52.00-74.00)	62.00 (51.50-73.00)	0.643
Alanine aminotransferase (U/L)	20.00 (14.00-29.00)	19.00 (14.00-27.69)	21.00 (13.50-29.00)	0.622
Aspartate aminotransferase (U/L)	28.00 (21.00-38.00)	28.00 (21.00-37.00)	27.00 (21.00-41.50)	0.898
Kalium (mmol/L)	3.94 (3.62-4.22)	3.94 (3.61-4.24)	3.93 (3.63-4.16)	0.585
Natrium (mmol/L)	140.00 (138.00-142.00)	140.00 (138.00-142.00)	140.00 (138.00-142.00)	0.983
Chlorine (mmol/L)	107.00 (104.00-109.00)	107.00 (104.00-109.00)	107.00 (104.00-109.00)	0.975
Alkaline phosphatase (U/L)	88.00 (66.00-123.00)	86.00 (66.00-121.00)	90.00 (67.00-136.50)	0.188
Glutamyl transferase (U/L)	38.00 (20.00-73.00)	37.00 (20.00-71.00)	41.00 (19.00-78.50)	0.533
Serum urea nitrogen (mmol/L)	4.91 (3.99-6.41)	4.97 (4.04-6.44)	4.78 (3.90-6.29)	0.326
Total protein (g/L)	66.10 (61.71-70.40)	66.03 (61.30-70.00)	66.47 (62.41-71.65)	0.121
Albumin (g/L)	35.73 (32.10-39.12)	35.80 (32.30-39.30)	35.50 (32.00-38.80)	0.297

International normalized ratio	1.27 (1.15-1.44)	1.27 (1.15-1.42)	1.30 (1.16-1.44)	0.280
Activated partial thromboplastin time (s)	33.40 (31.00-36.83)	33.50 (30.90-37.10)	33.20 (31.20-36.00)	0.554
Prothrombin time (s)	14.00 (12.70-15.72)	13.90 (12.70-15.50)	14.40 (12.80-16.00)	0.146
Prothrombin time activity (%)	66.00 (56.00-77.00)	67.00 (57.00-77.00)	65.00 (56.00-76.00)	0.334
Fibrinogen (g/L)	1.99 (1.57-2.50)	1.98 (1.56-2.48)	2.01 (1.62-2.54)	0.396
Blood ammonia (μmol/L)	42.64 (32.40-59.50)	42.30 (32.20-58.65)	43.40 (32.95-62.85)	0.360
White blood cell count ($\times 10^9$/L)	2.83 (1.90-4.19)	2.88 (1.90-4.14)	2.72 (1.86-4.23)	0.698
Hemoglobin ($\times 10^{12}$/L)	86.50 (74.00-104.00)	87.00 (74.00-104.00)	86.00 (75.00-104.00)	0.385
Platelet count ($\times 10^9$/L)	76.00 (50.00-121.00)	76.00 (50.00-116.00)	76.00 (52.00-123.50)	0.287
Alpha fetoprotein (ng/mL)	220.56 (2.85-423.31)	233.19 (2.88-413.82)	156.85 (2.66-428.81)	0.465
Carcinoembryonic antigen (ng/mL)	2.44 (1.62-3.61)	2.40 (1.63-3.54)	2.64 (1.60-3.75)	0.378
Carbohydrate antigen 125 (U/mL)	125.24 (36.20-233.29)	137.25 (40.10-242.69)	100.70 (33.20-204.23)	0.057
Cancer antigen 15-3 (U/mL)	10.30 (7.50-14.20)	10.30 (7.50-14.10)	10.40 (7.10-14.65)	0.604
Glycosylated chain antigen CA199 (U/mL)	10.94 (4.43-15.26)	11.47 (4.81-15.26)	9.26 (4.07-15.26)	0.179

MELD: Model for end-stage liver disease; TIPS: Transjugular intrahepatic portosystemic shunt; CA199: Carbohydrate antigen 199.

Table 5 Univariate and multivariate cox regression analyses of factors associated with mortality

Characteristics	Univariate analyses			Multivariate analyses		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Potassium	0.011	0.003-0.047	< 0.001[a]	0.030	0.007-0.122	< 0.001[c]
Creatinine	5.171	2.845-9.399	< 0.001[a]	1.947	1.114-3.404	0.019[b]
Alpha-fetoprotein	1.518	1.354-1.703	< 0.001[a]	1.455	1.298-1.631	< 0.001[c]
Portal vein diameter	0.078	0.035-0.172	< 0.001[a]	0.195	0.092-0.413	< 0.001[c]

[a]*P*< 0.01.
[b]*P*< 0.05.
[c]*P*< 0.01.
HR: Hazard ratio; CI: Confidence interval.

PHT, balancing portal pressure reduction with the risk of liver function deterioration, underscoring the complexity of PHT management[8,13,16]. Although emerging therapies such as selective β2-adrenergic receptor agonists and multikinase inhibitors have shown promise in reducing PHT, this study did not include patients receiving these treatments, as they were not widely adopted during the study period. Future research incorporating these novel therapies into predictive models could further refine risk stratification and optimize clinical decision-making[13]. The developed nomogram aligns with American Association for the Study of Liver Diseases-recommended PHT management strategies; however, regional variations in cirrhosis burden may influence its applicability[12]. For instance, cirrhosis-related mortality is highest in sub-Saharan Africa due to widespread viral hepatitis, whereas in Western countries, increasing HCC incidence is primarily linked to alcoholic liver disease and non-alcoholic fatty liver disease[27,29,30].

In this study, portal vein diameter, creatinine, potassium, and AFP were identified as key survival predictors after TIPS, consistent with existing findings[9,10,28,31]. Portal vein diameter is crucial for assessing PHT severity and is closely linked to prognosis[9,31]. Elevated creatinine indicates kidney dysfunction and may predict outcomes after TIPS[10,28]. Low potassium levels reflect electrolyte and acid-base imbalances[28]. Although AFP is traditionally considered an HCC marker, elevated AFP was associated with poorer survival after TIPS. This suggests that AFP may not only indicate HCC but also reflect liver function and inflammatory responses, reinforcing its role as an inflammatory marker[32]. Furthermore, portal pressure gradient is a critical predictor of post-TIPS outcomes. In this study, AFP and serum creatinine were more relevant for predicting long-term survival. These differences may be attributed to variations in patient populations, timing of stent placement, and technical factors[20,24]. In this study, log transformation was applied to key variables to handle non-normal data and improve model robustness, thus improving predictive accuracy[10,28]. LASSO regression is highly effective in managing high-dimensional data and avoiding overfitting, making it widely used in biomedical research[23]. LASSO shrinks the coefficients of non-informative variables to zero *via* L1 regularization, retaining only the most predictive ones, which simplifies the model and enhances both interpretability and robustness[10,

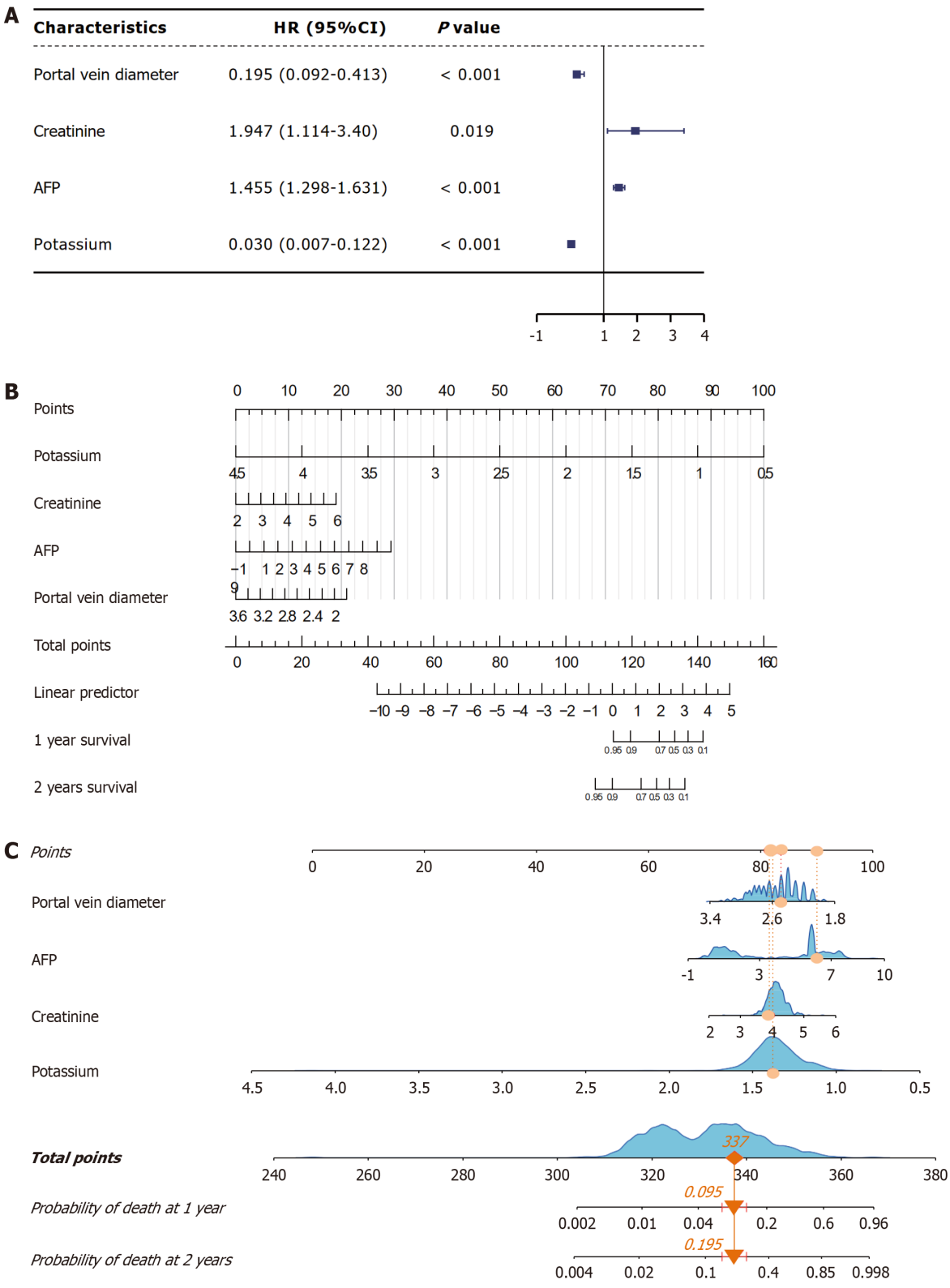


Figure 2 Prognostic model predicting the 1-year and 2-year survival following transjugular intrahepatic portosystemic shunt. A: Forest plot of multivariable Cox regression analysis showing hazard ratios with 95% confidence interval; B: Nomogram predicting the 1-year and 2-year survival probabilities; C: Nomogram with a patient case example, illustrating predicted mortality probabilities at 1 year and 2 years. HR: Hazard ratio; CI: Confidence interval; AFP: Alpha-fetoprotein.

20,23]. In this study, LASSO identified portal vein diameter, creatinine, potassium, and AFP as key variables, all of which showed significant independent prognostic value in Cox regression, consistent with previous findings on post-TIPS outcomes[28,33]. The developed model showed high discrimination ability and good calibration in training and validation sets, further demonstrating the utility of combining LASSO and Cox regression for handling complex datasets [10,20,23].

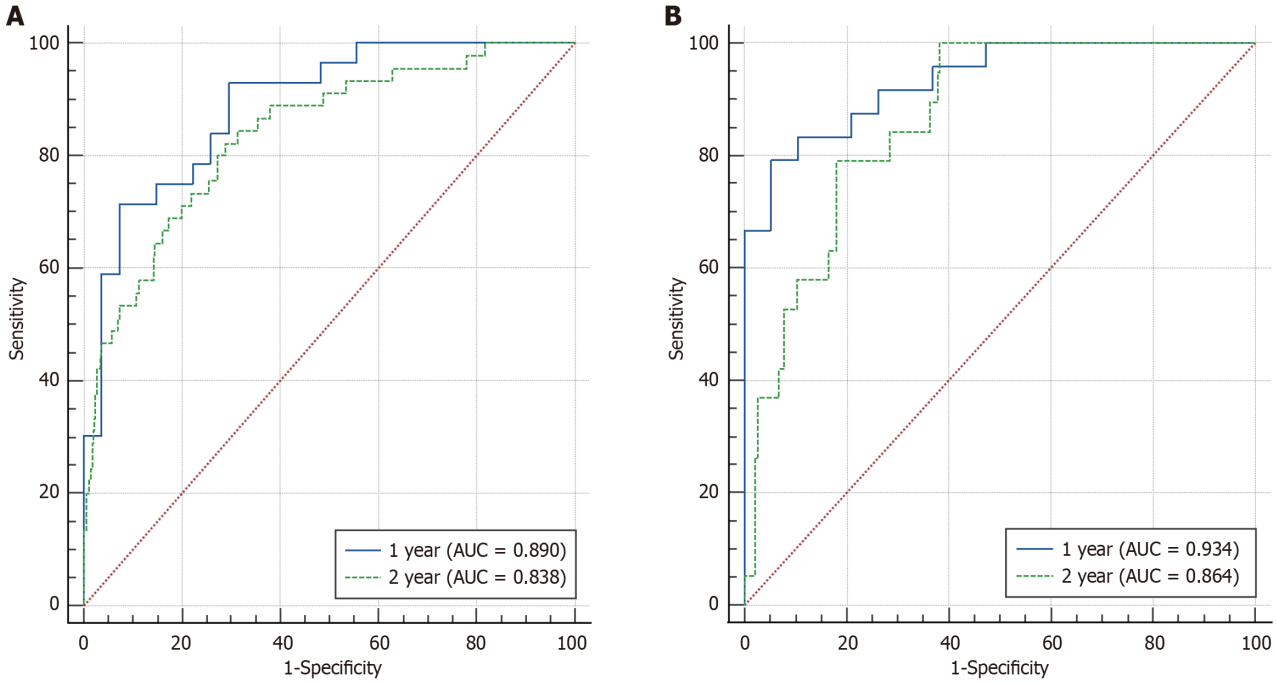


Figure 3 Receiver operating characteristic curves indicating the area under the curve for the nomogram model. A: Training set; B: Validation set. AUC: Area under the curve.

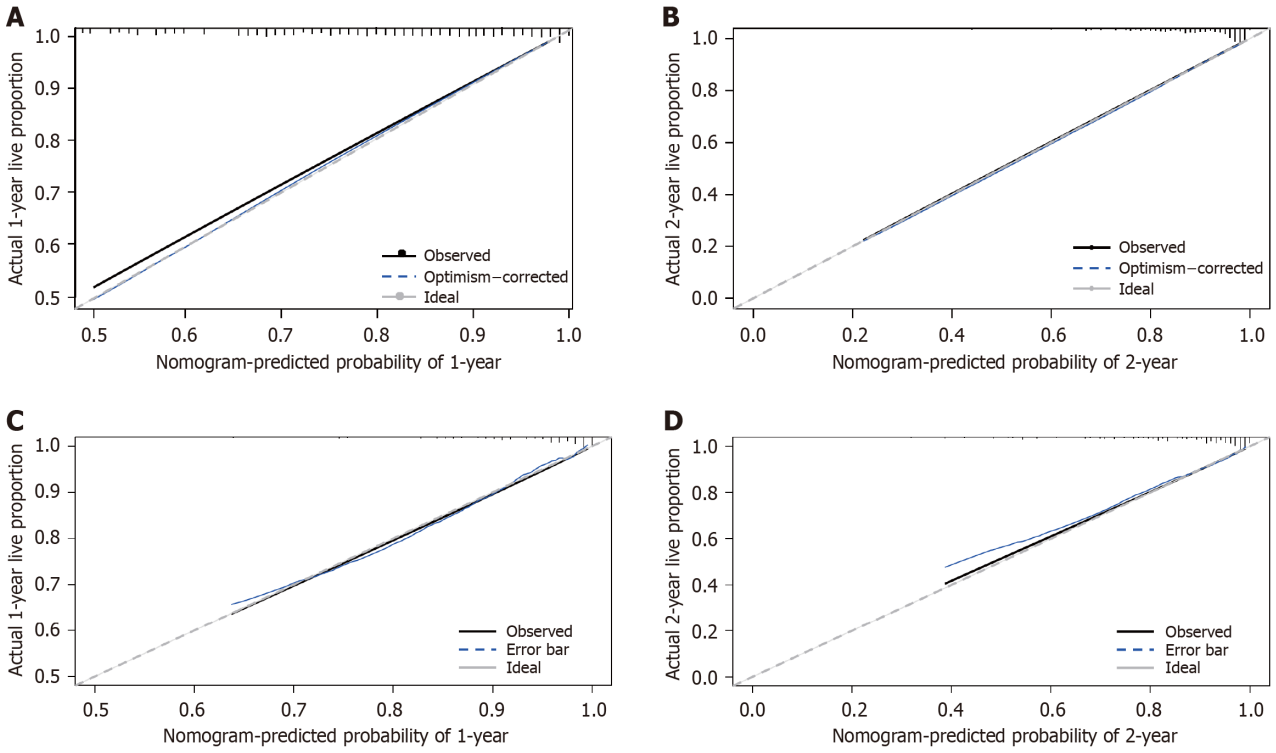


Figure 4 Calibration curves of the nomogram for predicting the 1-year and 2-year survival. A and B: Calibration curves of the nomogram for predicting the 1-year and 2-year survival in the training set; C and D: Calibration curves of the nomogram for predicting the 1-year and 2-year survival in the validation set.

Nonetheless, this study has some limitations. First, this is a retrospective study, and thus selection bias is inevitable. Additionally, the sample size may limit the generalizability of the model[20]. Besides, regional differences in cirrhosis and HCC risk factors may affect the model's applicability. For instance, 50%-60% of HCC cases in Eastern Europe are alcohol-related, compared to only 6%-14% in the Middle East and North Africa[27]. Therefore, localized adjustments should be applied to ensure accuracy. Nonetheless, further global studies are crucial to optimizing cirrhosis and PHT management strategies, which may enhance the model's applicability and clinical utility[29]. Although this study incorporated a broad

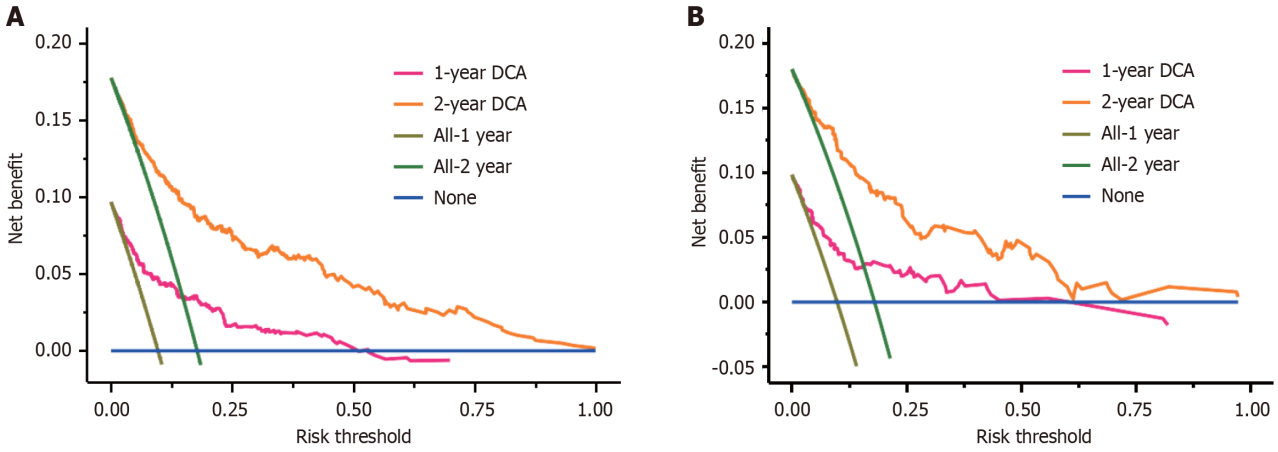


Figure 5 Decision curve analysis for the nomogram predicting the mortality. A: Decision curve analysis for the nomogram predicting the mortality in the training set; B: Decision curve analysis for the nomogram predicting the mortality in the validation set. DCA: Decision curve analysis.

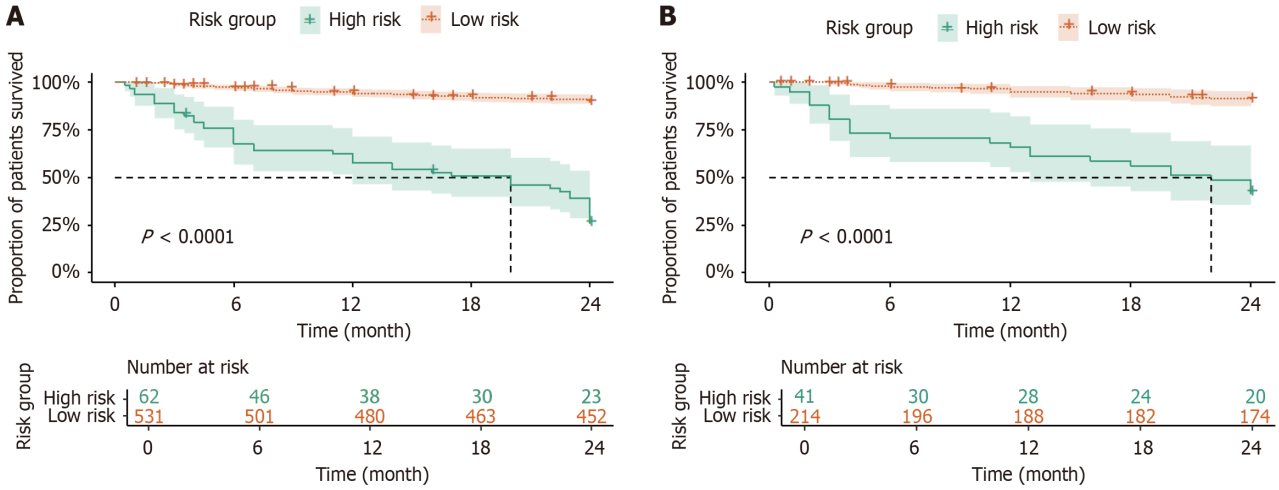


Figure 6 Kaplan-Meier survival curves comparing overall survival between high-risk and low-risk groups. A: Kaplan-Meier survival curves comparing overall survival between high-risk and low-risk groups in the training cohort; B: Kaplan-Meier survival curves comparing overall survival between high-risk and low-risk groups in the validation cohort.

range of cirrhosis-related factors into the model, key factors like genetic background and polymorphisms were not included, potentially affecting its predictive accuracy and external validity[23]. Therefore, future research should incorporate more population-specific characteristics and biomarkers to create more precise and personalized predictive models[33]. Future studies should also focus on several key areas to enhance the clinical applicability of the model. Prophylactic TIPS can significantly reduce rebleeding risk and improve long-term survival in high-risk patients, especially in patients with acute-on-chronic liver failure. Therefore, future work should clarify the indications for prophylactic TIPS and refine patient selection through individualized risk assessment to improve both procedure success and long-term survival[17,34]. One key limitation is that the follow-up period in this study was limited to two years, which may not fully capture long-term survival outcomes or late complications such as hepatic encephalopathy and shunt dysfunction. While our model provides robust survival predictions within this timeframe, future studies should explore its applicability beyond two years, incorporating long-term follow-up data to assess dynamic prognostic factors influencing survival. Additionally, exploring the impact of evolving therapies and personalized treatment approaches on long-term outcomes will be crucial for refining predictive models and improving clinical decision-making in TIPS patients[35].

CONCLUSION

Accurate postoperative survival prediction has become a key concern in clinical practice. In this study, a nomogram model was developed to predict survival in TIPS patients by combining LASSO and Cox regression models. While the model showed promising potential in clinical applications, its generalizability and accuracy should be further validated in diverse populations. Therefore, future research should consider incorporating more biomarkers and genetic factors to

improve model prediction. In conclusion, developing more precise and personalized predictive tools is critical for improving long-term outcomes among TIPS patients.

FOOTNOTES

Author contributions: Wang ZB, Zhu B, Meng MM, and Wu YF collected the data; Zhang Y, Li DZ, and Tian H performed the data analysis; Wang FC, Lv YF, and Ye QX contributed to data interpretation; Wang ZB and Liu FQ drafted the manuscript; Liu FQ supervised the study and revised the manuscript; Wang ZB, Zhu B, Meng MM, Wu YF, Zhang Y, Li DZ, Tian H, Wang FC, Lv YF, Ye QX, and Liu FQ designed the research study; and all authors have read and approved the final version of the manuscript.

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Informed consent statement: Since this research project was conducted on the basis of patients' routine treatment surgeries, without any additional procedures and without causing harm to the patients' bodies, we adopted the waiver of informed consent in the clinical setting.

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

Data sharing statement: The dataset and statistical code are available from the corresponding author, Fu-Quan Liu, at lfuquan@aliyun.com upon reasonable request. Consent for data sharing was not obtained, but the presented data are anonymized, and the risk of identification is low.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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ORIGINAL ARTICLE

Retrospective Study

Comparison of outcomes of laparoscopic-assisted and total laparoscopic right hemicolectomy for right-sided colon cancer

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Abstract

BACKGROUND

Colon cancer is a significant health issue in China, with high incidence and mortality rates. Surgical resection remains the primary treatment, with the introduction of complete mesocolic excision in 2009 improving precision and outcomes. Laparoscopic techniques, including laparoscopic-assisted right hemicolectomy (LARH) and total laparoscopic right hemicolectomy (TLRH), have further advanced colon cancer treatment by reducing trauma, blood loss, and recovery time. While TLRH offers additional benefits such as faster recovery and fewer complications, its adoption has been limited by longer operative times and technical challenges.

AIM

To compare the short-term outcomes of TLRH and LARH for the treatment of right -sided colon cancer and explore the advantages and feasibility of TLRH.

METHODS

Clinical data from 109 right-sided colon cancer patients admitted between January 2019 and May 2021 were retrospectively analyzed. Patients were divided into an observation group (TLRH, n = 50) and a control group (LARH, n = 59). Study variables were operation time, intraoperative bleeding volume, postoperative hospital stays, length of surgical specimen, number of lymph nodes dissected, and postoperative inflammatory factor levels of the two groups of patients. The postoperative complications were analyzed and compared, and survival, recurrence, and remote metastasis rates of the two groups were compared during a 2-year follow-up period.

RESULTS
The TLRH group showed the advantages of reduced intraoperative bleeding, shorter hospital stays, and quicker recovery. Lymph node dissection outcomes were comparable, and postoperative inflammatory markers were lower in the TLRH group. Complication rates were similar. Short-term follow-up (2 years) revealed no significant differences in recurrence, metastasis, or survival rates.

CONCLUSION
Compared to LARH, TLRH offers significant advantages in terms of reducing surgical trauma, lowering postoperative inflammatory factor levels, and mitigating the impact on intestinal function. This approach contributes to a shorter hospital stay and promotes postoperative recovery in patients. The study suggests that TLRH may offer favorable outcomes for colorectal cancer patients.

Key Words: Laparoscopic complete mesocolic excision; Total laparoscopic right hemicolectomy; Laparoscopic-assisted right hemicolectomy; Right-sided colon cancer; Short-term outcomes

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Core Tip: This retrospective study compared the outcomes of total laparoscopic right hemicolectomy (TLRH) and laparoscopic-assisted right hemicolectomy in right-sided colon cancer patients. TLRH demonstrated the advantages of reduced intraoperative bleeding, shorter hospital stays, and lower postoperative inflammation, while maintaining similar outcomes in lymph node dissection and complication rate. Additionally, no significant differences were observed in survival, recurrence, or metastasis rates over a 2-year follow-up period. The findings suggest that TLRH is a feasible approach that minimizes surgical trauma and enhances postoperative recovery.

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INTRODUCTION

Colon cancer poses a significant health concern in China, ranking as the third most commonly diagnosed cancer, with an estimated incidence rate of 29.5 per 100000 individuals and a mortality rate placing it fifth in the country. Surgical resection remains the primary treatment for colon cancer patients. Traditionally, laparotomy was the standard approach. The introduction of the concept of complete mesocolic excision (CME) in 2009 significantly improved surgical precision [1]. By meticulously minimizing tumor spread and maximizing lymph node clearance, CME aims to enhance patient outcomes, potentially leading to decreased local recurrence rates and improved overall survival[2-4].

The evolution of surgical techniques has introduced laparoscopic approaches, including laparoscopic-assisted right hemicolectomy (LARH) and total laparoscopic right hemicolectomy (TLRH), marking substantial advancements in the field. These approaches offer notable benefits, such as minimized trauma, reduced bleeding, and faster recovery, compared to traditional methods. The safety and efficacy of laparoscopic-assisted colon resections were established through multiple randomized trials in the early 2000s, demonstrating advantages such as decreased morbidity, shorter hospital stays, reduced analgesia requirements, and quicker return of bowel function[5-7].

Advancements in patient outcomes continued with the introduction of TLRH, showcasing benefits such as decreased conversion rates, faster return of bowel function, shorter hospital stays, and reduced incisional hernia rates. Despite these advantages, the adoption of TLRH has been slow due to increased operative time and required technical skills[8]. This retrospective analysis assessed patients undergoing either TLRH or LARH. The study aimed to investigate various aspects, including lymph node harvest, surgical duration, intraoperative blood loss, postoperative hospital stay, time to the first flatus and defecation, as well as the incidence of complications. Additionally, the research endeavored to compare the short-term outcomes between LARH and TLRH in individuals diagnosed with colon cancer.

MATERIALS AND METHODS

Study design

This retrospective study was conducted to compare the short-term outcomes of LARH and TLRH. Ethical approval for the study was obtained from the Liaocheng People's Hospital Ethics Committee (approval No. 2022173), and all methods were performed in accordance with the relevant guidelines and regulations. Due to retrospective study design, informed consent was waived by Liaocheng People's Hospital Ethics Committee.

Inclusion criteria

The inclusion criteria of the present study were as follows: (1) Patients who were diagnosed with right-sided colon cancer *via* preoperative imaging, colonoscopy biopsy, and postoperative routine histopathology, without distant metastasis; and (2) Patients with complete clinical data and normal functioning of key organs.

Exclusion criteria

Patients were excluded from the present study according to the following criteria: (1) A history of emergency surgeries due to tumors complicated with perforation, bleeding, and obstruction; (2) Distant metastasis observed before the surgery; and (3) A history of previous abdominal surgery or emergency surgery, and patients who underwent preoperative chemoradiotherapy. The study enrolled a total of 109 patients between 2019 and 2021. Among these, 50 patients underwent TLRH, constituting the observation group (TLRH), while 59 patients underwent LARH, forming the control group (LARH).

Laparoscopic CME surgical methods

Both surgical methods were completed in accordance with the total mesorectal excision and tumor-free principle. In both groups, all vascular ligations, lymph node dissections, and bowel mobilizations were performed laparoscopically within the abdominal cavity. In the TLRH group, after bowel mobilization and lymph node dissection, the bowel resection and digestive tract reconstruction were completed intracorporeally. In the LARH group, however, bowel resection and digestive tract reconstruction were performed extracorporeally. The specific steps are as follows:

Based on the principles of CME, a central approach was selected. The posterior peritoneum was opened along the surface of the superior mesenteric vein to enter the Toldt's space. The ileocolic vessels, right colic vessels (if present), right branches of the middle colic vessels, and accessory right colic veins were exposed, ligated, and divided. Corresponding lymphatic tissues at the vascular roots were cleared. Dissection proceeded laterally along the Toldt's fascia to the right paracolic gutter, while carefully protecting the right gonadal vessels, ureter, and head of the pancreas/duodenum. The terminal ileal mesentery, ascending colonic mesentery, and right transverse mesocolon were fully mobilized. The lateral peritoneum was opened from the ileocecal region along the right paracolic gutter to the hepatic flexure of the colon. The colon was separated from the retroperitoneum in a lateral-to-medial direction until it met the medial dissection plane. At the mid-transverse colon, the gastrocolic ligament was opened. The ligament was divided lateral to the gastroepiploic vessels. Adhesions between the gallbladder and colon were separated, and the hepatocolic ligament was divided. The transverse colon and ascending colon mesentery were freed from the head to the tail until they joined the medial dissection plane. In the TLRH group, the surgery continued intracorporeally. The ileum was divided 15 cm from the ileocecal junction using a Echelon® 60 mm linear stapler with a blue staple cartridge (Ethicon Endo-Surgery, United States). The colon was divided at the mid-right transverse colon using the same stapling device. The terminal ileum, cecum, ascending colon, right transverse colon, and part of the greater omentum were completely resected and placed in a specimen bag. The bowel ends were aligned, and the ileum was sutured and fixed to the distal colon approximately 7 cm from the proximal transected end. The blood supply to both ends was checked, and the tension at the anastomosis site was evaluated. Small incisions (1 cm each) were made on the opposite mesenteric side of the proximal and distal ends of the bowel. The intestinal lumen was disinfected with iodine-soaked gauze. The side-to-side ileocolic anastomosis was performed using a linear stapler. After ensuring no bleeding, the common opening was sutured with 2-0 unidirectional barbed suture to complete the anastomosis. The specimen was removed through the upper midline incision. In the LARH group, a midline longitudinal incision was made in the upper abdomen, and the incision was protected with a protective sheath. The tumor and the connected intestinal segment were brought outside the abdominal wall. The ileum was divided and closed 15 cm from the ileocecal junction, and the colon was divided and closed at the mid-right transverse colon. After removing the right hemicolon, an end-to-side anastomosis was performed between the remaining ileum and colon.

Data collection and observation indicators

Various parameters were meticulously collected and compared between the two groups. Duration of surgery, resected specimens, the number of lymph nodes dissected, postoperative inflammatory tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) levels, and complication rates were recorded in both the observation group and control group. Statistical analyses of recurrence rate and mortality rate during a 2-year follow-up period were conducted, and data were compared between the two groups.

Inflammatory factor evaluation

In our pursuit of understanding the nuanced differences between LARH and TLRH, we conducted an in-depth analysis of inflammatory factors. We measured the levels of TNF-α and CRP. These measurements were taken prior to surgery and at postoperative intervals of 1 days and 3 days.

Statistical analysis

Statistical analyses were performed using SPSS 23.0. Continuous variables are expressed as the mean ± SD and were compared using the *t* test. Categorical variables are presented as [*n* (%)] and were compared using the χ^2 test or rank-sum test. *P* values < 0.05 were considered indicative of statistically significant differences. The missing data were addressed through appropriate statistical methods or imputation techniques.

RESULTS

A total of 109 cases were included in this study. After thorough statistical analysis, the study revealed no significant differences in age, sex, body mass index, tumor stage, or accompanying diseases between the two groups. The observation group included 23 males and 27 females, with a mean age of (55.37 ± 9.65) years. The tumor-node-metastasis stage distribution was as follows: 5 cases at stage I, 14 at stage II, and 31 cases at stage III. The control group had 29 males and 30 females, with a mean age of (52.37 ± 8.35) years. Tumor-node-metastasis stage distribution in this group was 7 cases at stage I, 22 cases at stage II, and 30 cases at stage III (Table 1).

Comparison of relevant indexes between the two groups

The duration of surgery in the observation group (TLRH) was longer than that of the control group (LARH), the intraoperative bleeding in the observation group was lower than that of the control group, and hospital stays, postoperative drainage time, and anal exhaust time were shorter in the observation group. Specific comparison values are displayed in Table 1.

Comparison of inflammatory factor levels between the two groups

Before surgery, there were no statistically significant differences in the levels of TNF-α or CRP between the two groups, indicating comparability at baseline. However, on both the first and third days following surgery, a noticeable shift was observed. In the observation group, the levels of TNF-α and CRP consistently remained lower than those in the control group, and this difference reached statistical significance (Table 2). This temporal pattern suggests a distinct postoperative immunological response in the observation group, reinforcing the potential impact of the surgical intervention on inflammatory markers.

Comparison of complications between the two groups

The comparison of complications between the two groups revealed that there was no statistically significant difference in the rate of incision infection, lung infection, intestinal obstruction, or anastomotic leakage. The observation group demonstrated a lower incision infection rate compared to the control group, which may be attributed to the smaller incision size (Table 3).

Comparison of incidence, recurrence, and mortality rates between the two groups

There were no statistically significant differences in the recurrence rate or distant metastasis rate between the observation group and the control group during the 2-year follow-up period (Table 4). Additionally, the survival rate of patients in the observation group showed no significant difference compared to that of the control group (Figure 1).

DISCUSSION

The incidence of colon cancer, especially right-sided cases, has been steadily rising in recent years[9]. Surgical resection remains a critical component of treatment, with laparoscopic right hemicolectomy emerging as a preferred minimally invasive option over traditional laparotomy. This technique not only reduces trauma and stress responses but also facilitates faster postoperative recovery. Furthermore, it maintains the structural integrity of the mesocolon and anterior renal fascia, which improves procedural safety and allows for more accurate lymph node dissection aided by enhanced anatomical visualization. Laparoscopic CME has emerged as a low-trauma, minimally invasive alternative for managing right-sided colon cancer[10,11]. Numerous studies, including those by Sheng *et al*[12] and Huang *et al*[13], have validated the safety and efficacy of laparoscopic CME. This approach achieves outcomes comparable to open surgery in terms of radical resection and short-term survival. Notable benefits include faster recovery, reduced intraoperative bleeding, shorter hospital stays, and more extensive lymph node dissection[14-16]. Further research has consistently confirmed the feasibility and clinical advantages of laparoscopic CME[17,18]. Evidence from prior studies suggests that CME significantly enhances the prognosis of colon cancer patients. For instance, patients undergoing CME achieved a 4-year disease-free survival rate of 85.8%, compared to 75.9% in the traditional surgery group (P = 0.001)[19]. Similarly, Jeong *et al*[20] reported an improvement in the 5-year survival rate, rising from 78.1% (1984-2006) to 89.1% (2002-2016) following CME. These findings underscore the oncological benefits of CME, particularly in improving disease-free and overall survival outcomes.

A study highlights notable improvements in intraoperative blood loss, postoperative hospital stay duration, time to anal exhaust, and the number of lymph nodes dissected in laparoscopic CME for right-sided colon cancer[21]. The visual magnification provided by the laparoscope ensures a clear surgical pathway, a broader field of view, enhanced anatomical identification, reduced blood loss, and prevention of organ injury, all of which contribute to a smoother recovery[22]. Additionally, this approach significantly reduces stress responses and inflammation, as demonstrated by lower levels of inflammatory markers.

The approach to intracorporeal anastomosis in laparoscopic right hemicolectomy has undergone significant evolution. Historically, LARH with extracorporeal anastomosis was widely practiced. However, concerns over increased risk and technical challenges drove the exploration of totally laparoscopic techniques. In laparoscopic-assisted procedures, tissue dissection was performed laparoscopically, but anastomosis was completed extracorporeally. This technique, first introduced by Estour in 1993, was later standardized by Senagore and Nelson in 2004, with additional refinements by Estour in 2011[23]. Recent studies have highlighted challenges with extracorporeal anastomosis, such as requiring greater

Table 1 General clinical data and surgery-related indexes of the two groups (*n* = 109), mean ± SD

Basic information		Observation group (*n* = 50)	Control group (*n* = 59)	*P* value
Sex	Male	23	29	0.743
	Female	27	30	
Age (years)	< 60 years	30	35	0.943
	≥ 60 years	20	24	
TNM stage	I	5	7	0.744
	II	14	22	
	III	31	30	
Accompanying diseases	High blood pressure	13	18	0.603
	Diabetes	6	8	0.808
	Coronary heart disease	5	5	0.783
BMI (kg/m^2)		24.69 ± 5.71	25.66 ± 6.06	0.393
Operation time (minutes)		171.1 ± 11.0	161.4 ± 9.1	0.000
Intraoperative blood volume (mL)		154.6 ± 21.9	179.8 ± 23.5	0.000
Postoperative hospital stays (days)		6.43 ± 0.63	7.59 ± 2.19	0.000
Postoperative drainage time (days)		5.18 ± 0.40	5.31 ± 0.78	0.296
Time to anal exhaust (days)		2.49 ± 0.33	2.68 ± 0.31	0.004
Length of resected specimens (cm)		37.8 ± 1.5	38.3 ± 1.6	0.083
Average number of lymph nodes dissected		25.8 ± 2.4	25.9 ± 1.6	0.691

TNM: Tumor-node-metastasis; BMI: Body mass index.

Table 2 Comparison of inflammatory factor levels between the two groups, mean ± SD

Group	TNF-α (ng/mL)			CRP (ng/mL)		
	Preoperative	1 day after operation	3 days after operation	Preoperative	1 day after operation	3 days after operation
Observation group	8.04 ± 0.71	57.47 ± 2.19	12.14 ± 0.24	17.23 ± 1.36	160.40 ± 9.64	81.43 ± 4.26
Control group	10.25 ± 1.15	58.60 ± 1.91	30.21 ± 1.42	16.98 ± 4.36	165.18 ± 11.2	108.54 ± 3.24
P value	0.739	0.025	0.000	0.172	0.013	0.000

TNF-α: Tumor necrosis factor-α; CRP: C-reactive protein.

Table 3 Complications of patients with right-sided colon cancer in the two groups, *n* (%)

Group	Intestinal obstruction	Anastomotic leakage	Incision infection	Lung infection	Total
Observation group (*n* = 50)	2 (4.0)	2 (4.0)	2 (4.0)	6(12)	12 (24.0)
Control group (*n* = 59)	3 (5.0)	1 (1.7)	7 (11.9)	8(13.6)	19 (32.2)
P value	1.000	0.884	0.255	0.808	0.344

transverse colon mobilization, which can increase the risk of postoperative bleeding. By contrast, TLRH, introduced by Azagra in 1994 and standardized by Ghavami in 2008, performs both tissue dissection and anastomosis intracorporeally. While critics argue that this approach's increased technical complexity may lead to higher complication rates and longer operative times, advancements in stapling and suturing technology have greatly streamlined intracorporeal procedures, reducing these risks and improving surgical efficiency.

Table 4 Comparison of distant metastasis rate, recurrence rate, and mortality between the two groups, *n* (%)

Group	Distant metastasis incidence rate at 2 years	Recurrence rate at 2 years	Mortality at 2 years
Observation group	7 (14.0)	8 (16.0)	6 (12.0)
Control group	9 (15.3)	11 (18.6)	10 (16.9)
P value	0.854	0.717	0.467

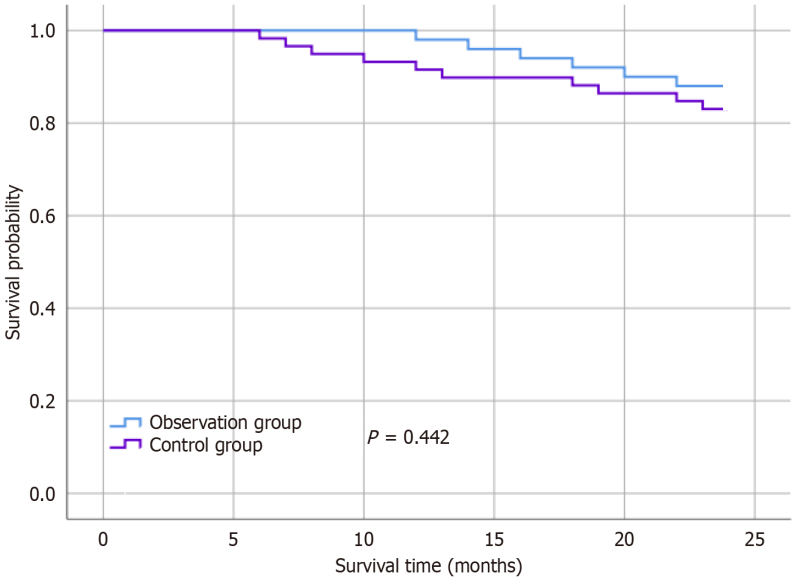


Figure 1 Overall survival rates in the observation group and control group. *P* value: Kaplan-Meier/Log-Rank test.

The comparable surgical specimen length and number of dissected lymph nodes between the TLRH and LARH groups underscore the surgical proficiency in achieving oncological objectives. The longer total operation time and anastomosis time in the TLRH group, mitigated by fewer instances of intraoperative bleeding, shorter postoperative hospital stays, and reduced postoperative anal exhaust time, necessitate a nuanced interpretation. The extended operative times may reflect the complexity of TLRH, potentially requiring meticulous surgical techniques. However, the reduced bleeding in TLRH aligns with studies associating minimized blood loss with improved recovery. The shorter postoperative parameters in the TLRH group suggest potential benefits in terms of patient comfort and healthcare resource utilization. Compared to TLRH, LARH often requires more extensive bowel mobilization to extract the intestine through the small incision. In patients with large tumors or significant intra-abdominal fat, this may necessitate enlarging the skin incision, potentially causing excessive traction on the bowel and increasing the risk of colon or mesentery damage. In contrast, intracorporeal anastomosis can mitigate these challenges by minimizing incision size and enhancing the overall minimally invasive nature of the procedure. The corresponding decrease in postoperative levels of TNF-α and CRP in the TLRH group implies a mitigated inflammatory cascade, potentially influencing early recovery and reducing the risk of inflammatory-related complications. While the overall complication rate is comparable, the trend towards a lower incision infection rate in the TLRH group, albeit not statistically significant, underscores the potential benefits of smaller incisions. Minimizing incision-related complications is critical to improving the safety and recovery of patients undergoing minimally invasive procedures. The 2-year follow-up data revealed no significant differences in survival, recurrence, or distant metastasis rate between TLRH and LARH, confirming their oncological equivalence. These findings are consistent with the existing literature, which supports the safety and efficacy of both approaches in delivering comparable oncological outcomes. Clinicians can be reassured that short-term differences in outcomes, such as reduced bleeding and faster recovery with TLRH, do not compromise the long-term integrity of either surgical method. These findings hold practical implications for clinical decision-making. Surgeons may consider the nuanced advantages of TLRH, such as reduced bleeding and shorter hospital stays, particularly in patients where minimizing these factors is crucial. The lack of significant differences in short-term oncological outcomes ensures that both TLRH and LARH remain viable options, allowing for individualized treatment plans tailored to patient-specific considerations.

CONCLUSION

In conclusion, TLRH demonstrates significant benefits, including reduced surgical trauma, lower postoperative inflammatory factor levels, and less impact on intestinal function compared to LARH. This approach results in a shorter hospital

stay and facilitates postoperative recovery. In summary, our study highlights the advantages of TLRH over LARH, showcasing comparable postoperative complication rates. Both procedures exhibit similar short-term outcomes in terms of survival, recurrence, and distant metastasis rates. Considering these findings, TLRH emerges as a preferable option for patients undergoing right-sided colon cancer surgery. These insights contribute to informed clinical decision-making and potential refinements in treatment protocols for individuals with right-sided colon cancer. Our results suggest that TLRH is a safe and feasible approach for treating right-sided colon cancer, emphasizing the need for further research to comprehensively validate these findings.

FOOTNOTES

Author contributions: Du WF and Yang CG designed the research protocols for the present study, and provided guidance for writing and revising the article; Liang TS wrote the article and conducted the statistical analyses; Guo ZF collected the clinical data and abstracted the data; Li JJ participated in modification and data analysis; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Single-incision laparoscopic herniorrhaphy needle treatment for pediatric inguinal hernia: Surgical outcome, postoperative complications, and serum inflammation effects

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Abstract

BACKGROUND

Laparoscopic surgery, with the advantage of less trauma, has been predominantly performed to treat pediatric inguinal hernia. However, the traditional three-port laparoscopic surgery remains extremely traumatic for children, whereas single-port laparoscopic surgery causes less damage to children than traditional laparoscopy. However, single-port laparoscopic surgery is more challenging; thus, studies on the effect of its application in pediatric inguinal hernia remain relatively limited.

AIM

To analyze the association of single-incision laparoscopic herniorrhaphy needle treatment with surgical outcomes, postoperative complications, and serum inflammation in pediatric inguinal hernia.

METHODS

This retrospective study included 113 pediatric patients with inguinal hernia who underwent surgery at the Children's Hospital, Capital Institute of Pediatrics, from April 2022 to May 2023. Participants were categorized into the observation group (single-incision laparoscopic herniorrhaphy needle, n = 60) and the control group (two-port laparoscopic surgery, n = 53). Comparative analyses involved surgical duration, intraoperative blood loss, and length of hospital stay. C-reactive protein (CRP) and white blood cell count (WBC) levels were measured preoperatively and 24 hours postoperatively. Postoperative pain was evaluated with the face, legs, activity, cry, and Consolability scale. Further, the incidence of complications, recurrence, and reoperation rates was assessed. Logistic regression was employed to determine independent risk factors related to poor prognosis.

RESULTS
The observation group demonstrated significantly reduced intraoperative blood loss and shorter hospitalization compared to the control group ($P < 0.05$). Both groups demonstrated increased CRP and WBC levels postoperatively, but the observation group exhibited significantly lower levels ($P < 0.05$). Further, pain scores at 24 hours postoperatively were significantly lower in the observation group ($P < 0.05$). Additionally, the observation group experienced fewer adverse events, recurrence rates, and reoperations compared to the control group ($P < 0.05$). Logistic regression analysis determined increased postoperative stress markers and surgical technique as independent predictors of recurrence ($P < 0.05$).

CONCLUSION
Single-incision laparoscopic herniorrhaphy needle treatment for pediatric inguinal hernia exhibits significant efficacy, effectively reduces postoperative complications, ensures a more concealed surgical incision, and promotes faster postoperative recovery than conventional two-port laparoscopy. This approach merits wider application.

Key Words: Single-incision laparoscopic herniorrhaphy needle; Pediatric inguinal hernia; Surgical outcome; Postoperative complications; Serum inflammation

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Core Tip: Single-port laparoscopic hernia needle treatment of inguinal oblique hernia is less harmful to children and is conducive to their recovery immediately after surgery. A single-port laparoscopic hernia needle exhibits a milder inflammatory state than the two-port laparoscopy, with fewer adverse reactions. Increased postoperative stress indexes and surgical procedures are independent risk factors for recurrence in children.

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INTRODUCTION

Pediatric indirect inguinal hernia is a prevalent clinical condition, particularly during the neonatal period. This condition originates from the underdeveloped and weakened abdominal wall structures in neonates. Activities that increase intra-abdominal pressure, such as crying or defecation, facilitate the descent of intestinal tissues into the scrotum, thereby forming an inguinal hernia[1,2]. Epidemiological data indicate a male-to-female incidence ratio of approximately 15: 1, with a higher prevalence on the right side. The primary etiological factor includes the congenital failure of the processus vaginalis to undergo complete closure[3]. Surgical intervention is the primary treatment for this condition. Without timely management, the hernia may progressively enlarge with the child's growth, thereby increasing the risk of severe complications. These complications include herniated content incarceration, which causes ischemia of the intestines and omentum. This may progress to necrotizing bowel obstruction in extreme cases, posing significant morbidity risks[4,5].

In recent years, the continuous evolution of minimally invasive techniques has resulted in the widespread adoption of laparoscopic surgery in managing pediatric indirect inguinal hernia. This approach not only facilitates the determination of contralateral occult hernias but also significantly reduces surgical trauma, which provides improved protection of important structures, such as the fallopian tubes and spermatic vessels, thereby minimizing bodily harm[6,7].

However, traditional laparoscopic procedures typically require either three (a primary operative port, an auxiliary port, and an observation port) or two incisions (a primary operative port and an observation port), which still causes notable trauma for pediatric patients[8]. In contrast, single-port laparoscopic surgery, which involves a single small incision without additional ports, provides several advantages, including reduced trauma, accelerated postoperative recovery, and improved surgical outcomes. Hence, this technique has been gradually accepted in clinical practice[9].

Emerging evidence confirms the efficacy of single-port laparoscopic surgery in treating patent processus vaginalis in pediatric patients. In particular, previous studies have revealed its favorable therapeutic outcomes[10]. However, the procedure presents significant technical challenges, and research on its application for pediatric indirect inguinal hernia remains relatively limited, emphasizing the need for further investigation and improvement of this promising approach.

This study investigated the association of single-port laparoscopic hernia needle surgery with surgical outcomes, postoperative complications, and serum inflammatory markers in pediatric patients with indirect inguinal hernias to provide valuable reference data for its future clinical application.

MATERIALS AND METHODS

Clinical data

This study retrospectively analyzed 113 pediatric patients with indirect inguinal hernia undergoing surgical treatment at Children's Hospital Capital Institute of Pediatrics from April 2022 to May 2023. Patients were categorized based on surgical approach into the observation group (treated with a single-port laparoscopic hernia needle, n = 60) and the control group (treated with the two-port laparoscopic method, n = 53).

Inclusion criteria were patients: (1) Who were clinically diagnosed with indirect inguinal hernia through ultrasound examination; (2) Who had unilateral hernia; (3) Who met the surgical treatment standards; and (4) Who had complete medical records. Exclusion criteria were patients: (1) Who did not meet surgical treatment standards; (2) Who had severe hepatic or renal dysfunction; (3) Who were diagnosed with other malignant tumors; and (4) Who had immune deficiency disorders.

Surgical procedure

All patients underwent comprehensive preoperative assessments, including blood tests, coagulation tests, cardiac ultrasound, electrocardiogram, and chest X-ray. This study excluded patients who did not meet surgical treatment criteria. All patients received general anesthesia in a supine position. A 0.5-cm incision was created at the umbilicus, through which a 5-mm Trocar was inserted to establish pneumoperitoneum with an intra-abdominal pressure maintained at 8-10 mmHg, which served as the observation port.

The control group underwent two-port laparoscopic treatment. A 3-mm incision was created on the right abdominal wall near the umbilicus or slightly lower. A 2-0 non-absorbable suture with a needle was used to puncture the peritoneum under the thin right abdominal wall. The needle was guided through the peritoneum's outer interlayer using an operating clamp, which encircles once around the internal ring, thereby expelling gas from the hernia sac. The suture was tightened and tied distally after ensuring complete closure of the internal ring. The umbilical incision was sutured, and the other incision was closed with adhesive tape to reduce tension and prevent scar hyperplasia.

Patients in the observation group underwent single-incision laparoscopic herniorrhaphy using a specialized needle technique. The procedure started by creating a 1-mm incision at the projected location of the internal inguinal ring on the abdominal wall. A dura mater puncture needle preloaded with a 2-0 non-absorbable suture was inserted perpendicularly through the incision, which advanced to the outer interlayer of the peritoneum. The needle was guided beneath the fallopian tube and spermatic vein to pierce the peritoneum, leaving the suture within the abdominal cavity.

The needle was then carefully withdrawn to the outer interlayer of the peritoneum and reinserted through the opposite side of the internal ring. The suture was retrieved and pulled out of the body to achieve a complete internal inguinal ring closure while ensuring proper air evacuation from the hernia sac. The suture was securely tied externally, with the ends buried subcutaneously. To evaluate for contralateral occult hernias, the procedure was repeated if required. The laparoscope was removed after confirming the absence of bleeding points, and the umbilical incision was then meticulously sutured. The small incision at the internal ring site required no suturing due to its minimal size.

Both the observation and control groups received standardized postoperative care, which included rehabilitation training, pharmacological interventions, and other management measures, to ensure optimal recovery.

Observation indicators

(1) Surgical parameters: Surgical duration, intraoperative blood loss, and hospital stay were compared between the two pediatric cohorts; (2) Stress response indicators: C-reactive protein (CRP) and white blood cell (WBC) levels were measured preoperatively and 24 hours postoperatively for both groups; (3) Pain assessment: Postoperative pain was assessed using the face, legs, activity, cry, and Consolability scale[11], which evaluates five behavioral indicators-facial expression, leg movement, activity level, crying, and consolability-each scored on a 0-2 scale, with a total score ranging from 0 to 10. Scores of > 7 indicate severe pain, 3-7 denote moderate pain, and < 3 represent mild pain; (4) Postoperative complications: The occurrence of postoperative complications, including incision infections, scrotal edema, hydrocele, and subcutaneous edema, was recorded and compared between groups; (5) Follow-up analysis: A 6-month follow-up was conducted to evaluate and compare recurrence and reoperation rates between the two groups; and (6) Prognostic evaluation: Patients were categorized into good and poor prognosis groups based on recurrence outcomes. Logistic regression analysis was conducted to determine independent predictors of poor prognosis.

Statistical analysis

Statistical package for the social sciences version 19.0 software was used for statistical analysis, and GraphPad 7 software was utilized for graphical representation. Count data were expressed as percentages and analyzed using χ^2 tests. Further, intergroup comparisons were conducted using independent t-tests. Pre- and post-treatment comparisons were performed using paired t-tests. Logistic regression analysis was conducted to identify independent predictors of poor prognosis. Statistical significance was set at a P-value of < 0.05.

RESULTS

Comparison of general data

The two groups of pediatric patients demonstrated comparable baseline characteristics, with no statistically significant

differences in terms of gender, age, body mass index, or disease staging ($P > 0.05$, Table 1).

Comparison of surgical indicators

Surgical duration was not significantly different between the observation and control groups ($P > 0.05$). Conversely, patients in the observation group experienced significantly less intraoperative blood loss and shorter hospital stays than those in the control group ($P < 0.05$, Table 2).

Comparison of stress indicators

Preoperative CRP and WBC levels were comparable between the observation and control groups ($P > 0.05$). Both groups demonstrated higher CRP and WBC levels postoperatively than at baseline. However, the observation group demonstrated significantly lower CRP and WBC levels than the control group 24-hour postoperatively ($P < 0.05$, Figure 1).

Comparison of postoperative pain

The 24-hour postoperative pain score for the observation group was 1.15 ± 0.36 points, which was significantly lower than the control group at 2.49 ± 0.5 points ($P < 0.05$, Figure 2).

Comparison of postoperative complications

The observation group demonstrated significantly lower complication rates (5.00%) than the control group (22.64%, $P < 0.05$). Further, specific complications, which included incision infection, scrotal edema, scrotal effusion, and subcutaneous edema, occurred less frequently in the observation group (Table 3).

Comparison of recurrence and reoperation rates

A 6-month follow-up indicated significantly lower recurrence and reoperation rates in the observation group than in the control group ($P < 0.05$, Table 4).

Analysis of independent risk factors for recurrence

Pediatric patients were categorized into the good- and poor-prognosis groups based on recurrence status. Logistic regression analysis was conducted to identify independent risk factors related to poor prognosis. Univariate analysis revealed significant differences in terms of postoperative stress markers, and surgical technique between the two groups ($P < 0.05$, Table 5). These variables were further analyzed with a multivariate logistic regression model, which determined increased postoperative stress markers and surgical approach as independent predictors of recurrence ($P < 0.05$, Table 6).

DISCUSSION

Inguinal hernia, which includes direct and indirect hernias, is a prevalent condition in general surgery. Indirect inguinal hernias are particularly predominant in pediatric and young adult populations and are characterized by abdominal content protrusion through the inguinal canal, with potential extension into the scrotum. This makes them especially susceptible to complications such as incarceration[12]. Indirect inguinal hernia cannot resolve spontaneously and exhibits limited responsiveness to pharmacological treatment, requiring surgical intervention as the primary therapeutic approach, unlike some conditions. Traditional open abdominal surgery has been predominantly used, but it is associated with significant surgical trauma, which hinders recovery, particularly in pediatric patients[13].

The development and improvement of minimally invasive techniques have revolutionized the surgical management of pediatric indirect inguinal hernia. Laparoscopic surgery has been popular because of its multiple advantages, including reduced postoperative pain, smaller incisions, and improved preservation of critical anatomical structures such as the iliac and hypogastric nerves, spermatic vessels, inguinal nerves, and fallopian tubes[14,15]. Furthermore, laparoscopy provides the distinct advantage of determining occult hernias, thereby reducing the risk of missed diagnoses. One of the challenges in the surgical management of pediatric indirect inguinal hernia is the possibility of recurrence, which is largely affected by the completeness of internal inguinal ring closure. Laparoscopic surgery provides superior visualization of the spermatic cord and internal ring, thereby facilitating precise high hernial sac ligation. This improved accuracy not only enhances surgical outcomes but also minimizes recurrence rates.

This study assessed the efficacy and safety of single-port laparoscopic herniorrhaphy compared to conventional two-port laparoscopic surgery in pediatric patients with indirect inguinal hernia. The results revealed that the observation group undergoing single-port laparoscopic herniorrhaphy experienced significantly reduced intraoperative blood loss and shorter hospital stays than the control group, indicating that this approach causes less surgical trauma and promotes faster postoperative recovery.

The advantages of single-port laparoscopic herniorrhaphy originate from its minimally invasive design. Traditional two-port laparoscopic surgery involves inserting two to three trocars as operating and observation ports, which increases procedural complexity and associated tissue damage[16]. In contrast, the single-port technique uses a dura mater puncture needle for high hernial sac ligation, which consolidates the operating and observation functions into a single-port. This reduces trauma and visible scarring. Furthermore, the procedure requires only one trocar, and the laparoscope was used to magnify internal structures, enabling precise and efficient internal inguinal ring closure with circular sutures subcutaneously tied outside the body[17].

Table 1 Comparison of general data, *n* (%)

Variable	Observation group (*n* = 60)	Control group (*n* = 53)	χ^2	*P* value
Gender			0.022	0.883
Male	32 (52.33)	29 (54.72)		
Female	28 (46.67)	24 (45.28)		
Age (years)			0.228	0.633
≥ 7	29 (48.33)	28 (52.83)		
< 7	31 (51.67)	25 (47.17)		
BMI (kg/m^2)			0.029	0.864
≥ 18	33 (55.00)	30 (56.60)		
< 18	27 (45.00)	23 (43.40)		
Disease duration (years)			0.001	0.987
≥ 1	25 (41.67)	22 (41.51)		
< 1	35 (53.33)	31 (58.49)		
Affected area			0.006	0.939
Left side	31 (51.67)	27 (50.94)		
Right side	29 (48.33)	26 (49.06)		

BMI: Body mass index.

Table 2 Comparison of surgical indicators

Variable	Observation group (*n* = 60)	Control group (*n* = 53)	*t*	*P* value
Operation time	27.37 ± 1.03	27.16 ± 1.01	1.091	0.277
Intraoperative blood loss	3.3 ± 0.24	5.31 ± 0.25	43.57	< 0.001
Hospitalization time	2.13 ± 0.34	5.23 ± 0.47	40.49	< 0.001

Table 3 Comparison of adverse reactions, *n* (%)

Variable	Observation group (*n* = 60)	Control group (*n* = 53)	χ^2	*P* value
Wound infection	0	4 (7.55)	-	-
Scrotal edema	2 (3.33)	3 (5.66)	-	-
Scrotal effusion	1 (1.67)	3 (5.66)	-	-
Subcutaneous edema	0	2 (3.77)	-	-
Total incidence	3 (5.00)	12 (22.64)	7.608	0.006

Previous studies have reported the benefits of single-port laparoscopy in appendectomy, demonstrating shorter hospital stays and lower rates of wound infections compared to conventional methods[18]. These results are congruent with our conclusions, highlighting the advantages of single-port laparoscopic surgery. However, our study represents the first comprehensive and detailed evaluation of its application in pediatric indirect inguinal hernia. Some researchers have proposed bilateral approaches near the umbilicus to minimize visible scarring, but the proximity and parallel alignment of surgical instruments and the laparoscope pose technical challenges, thereby limiting its feasibility and broader clinical adoption. Therefore, the single-port approach provides a viable, efficient, and less invasive alternative for pediatric hernia repair.

Laparoscopic surgery is recognized for its minimally invasive nature while inevitably inducing various degrees of surgical trauma. The early inflammatory response serves as a crucial indicator of the extent of tissue injury. To further investigate the effect of single-port laparoscopic herniorrhaphy on pediatric patients, we compared stress biomarkers and postoperative complications between the observation and control groups.

Table 4 Comparison of recurrence and reoperation rates between the two groups of children, *n* (%)

Variable	Observation group (*n* = 60)	Control group (*n* = 53)	χ^2	*P* value
Recurrence	13 (21.67)	22 (41.51)	5.183	0.022
Second surgery	8 (13.33)	17 (32.08)	5.737	0.017

Table 5 Univariate analysis, *n* (%)

Variable		Good prognosis group (*n* = 78)	Poor prognosis group (*n* = 35)	χ^2	*P* value
Gender				0.739	0.390
	Male (*n* = 61)	40 (51.28)	21(60.00)		
	Female (*n* = 52)	38 (48.72)	14 (40.00)		
Age (years)				0.911	0.340
	≥ 7 (*n* = 57)	37 (47.44)	20 (57.14)		
	< 7 (*n* = 56)	41 (52.56)	15 (42.86)		
BMI (kg/m^2)				0.371	0.543
	≥ 18 (*n* = 63)	42 (53.85)	21 (60.00)		
	< 18 (*n* = 50)	36 (46.15)	14 (40.00)		
Disease duration (years)				0.033	0.855
	≥ 1 (*n* = 47)	32 (41.03)	15 (42.86)		
	< 1 (*n* = 66)	46 (58.97)	20 (57.14)		
Stress response index					
	CRP	11.48 ± 2.54	13.6 ± 2.47	4.137	< 0.001
	WBC	10.00 ± 1.45	11.47 ± 1.25	5.191	< 0.001
Surgical plan				5.183	0.023
	Two-port laparoscopic hernia needle (*n* = 53)	31 (39.74)	22 (62.86)		
	Single-port laparoscopic hernia needle (*n* = 60)	47 (60.26)	13 (37.14)		

CRP: C-reactive protein, WBC: White blood cell; BMI: Body mass index.

Table 6 Multivariate analysis

Variable	β	SE	Wals	*P* value	Exp(B)	95%CI	
						Lower limit	Upper limit
CRP	0.244	0.099	6.040	0.014	1.277	1.051	1.551
WBC	0.705	0.195	12.123	0.000	2.024	1.382	2.964
Surgical plan	-1.923	0.543	12.541	0.000	0.146	0.050	10.424

CRP: C-reactive protein, WBC: White blood cell.

CRP, a key acute-phase reactant that is synthesized in the liver, is significantly increased in response to stress stimuli [19]. Its levels correlate with acute tissue injury, where higher concentrations indicate greater damage. CRP levels decrease rapidly as inflammation resolves, making it a sensitive, although non-specific, marker for tissue injury[20,21].

WBCs, which are central to the immune response, contribute to both innate and adaptive immunity. Leukocyte extravasation is a hallmark of the inflammatory process[22]. Our results revealed that postoperative CRP and WBC levels increased significantly in both groups. However, these elevations were markedly lower in the observation group, indicating that both surgical approaches provoke inflammatory responses, but single-port laparoscopic herniorrhaphy

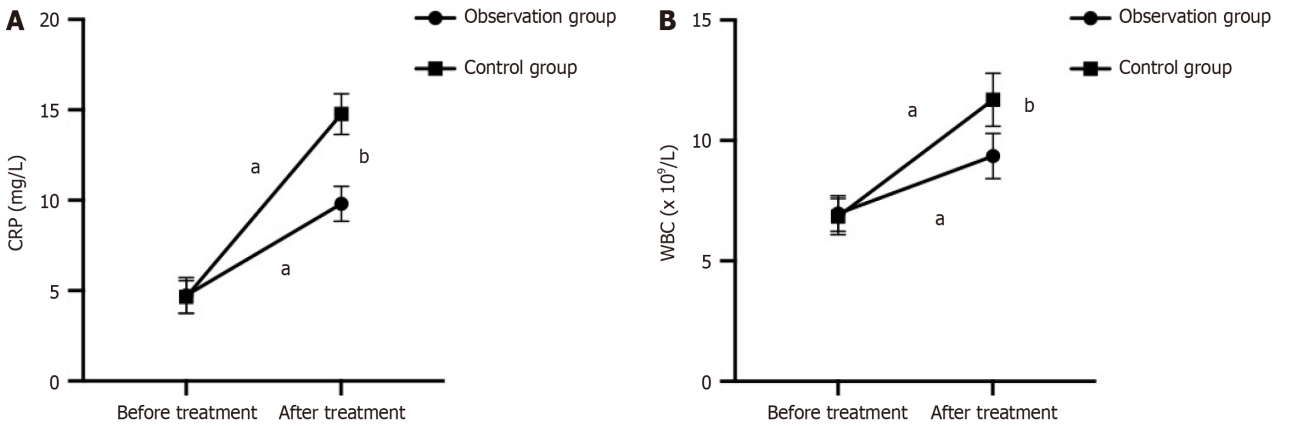


Figure 1 Comparison of stress indicators. A: Comparison of C-reactive protein levels before and after treatment in two groups; B: Comparison of white blood cell levels before and after treatment in two groups. $^{a}P < 0.05$ the group before *vs* after treatment. $^{b}P < 0.05$ between groups after treatment. CRP: C-reactive protein; WBC: White blood cell.

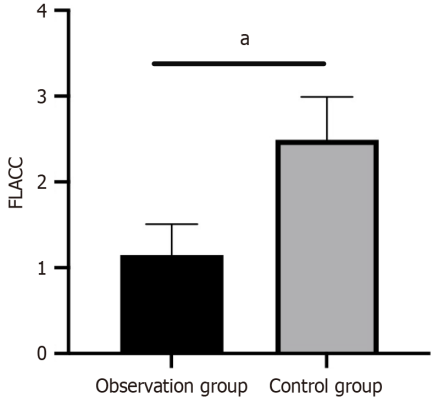


Figure 2 Comparison of postoperative pain between the two groups. FLACC pain assessment (face: Facial expression; legs: Leg activity; activity: Body position; cry: Crying; consolability: Consolability) was performed 24 hours after surgery. $^{a}P < 0.05$ for the comparison between the two groups.

exerts a milder inflammatory state. This attenuation may be related to the decreased number of surgical ports, causing less tissue trauma and a diminished stress response[23].

Furthermore, our results indicated significantly lower recurrence and reoperation rates in the observation group than in the control group. This indicates that both surgical techniques are effective in treating pediatric indirect inguinal hernia, but single-port laparoscopic herniorrhaphy provides superior outcomes in terms of recurrence and reoperation rates. The improved efficacy of single-port laparoscopic herniorrhaphy may originate from its ability to detect contralateral occult hernias and achieve a more comprehensive high hernial sac ligation, thereby reducing the risk of recurrence and the need for subsequent surgical interventions[24].

Finally, to further determine factors that affect prognosis, we categorized children into the good and poor prognosis groups based on recurrence and analyzed independent risk factors for recurrence. Increased postoperative stress indicators were considered independent risk factors for recurrence, possibly associated with increased infection, although the exact mechanism warrants further investigation. Conversely, single-port laparoscopic herniorrhaphy was an independent protective factor against recurrence.

CONCLUSION

In summary, single-port laparoscopic herniorrhaphy for pediatric indirect inguinal hernia exhibits significant efficacy, effectively reduces postoperative complications, provides more concealed incisions, and promotes faster recovery compared to conventional two-port laparoscopy. Thus, it is worth promoting. However, the study's limited sample size and single comparison method may introduce bias, requiring further research.

FOOTNOTES

Author contributions: Wang XQ designed the study; Wang XQ and Kong CH collected and analyzed the data; Wang XQ wrote the manuscript; Wang XQ and Kong CH revised the manuscript; Wang XQ and Kong CH participated in collection of the data; All authors approved the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Association of Sijunzi decoction plus chemotherapy with gastrointestinal function and serum markers in patients after gastric carcinoma surgery

Xiao-Dong Wang, Xiao-Qing Su, Hong Gao

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Abstract

BACKGROUND

The deleterious effects of surgical trauma and subsequent postoperative complications pose significant challenges to the smooth recovery of patients after gastric cancer (GC) resection despite the substantial curative benefits provided by surgical interventions for GC. Hence, the investigation of more optimal and efficacious treatment approaches has become an urgent necessity in the medical community.

AIM

To investigate the association of Sijunzi decoction plus chemotherapy with the gastrointestinal function and serum markers of patients after GC surgery.

METHODS

This study included patients who underwent GC surgery from June 2022 to February 2024. The control group included 45 patients who received chemotherapy (oxaliplatin + calcium folinate + 5-fluorouracil), whereas the research group consisted of 54 patients who received Sijunzi decoction therapy in addition to the treatment administered in the control group. Comparative analyses were conducted from the following perspectives: Gastrointestinal function (defecation time, intestinal gas discharge time, and hospitalization time), serum markers [carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125, and CA199], nutritional indicators [total protein (TP) and transferrin (TRF), traditional Chinese medicine (TCM) syndrome score, and grades III–IV adverse events (gastroin-

testinal reactions, renal/liver function impairment, and myelosuppression).

RESULTS

The two groups demonstrated similar defecation time ($P > 0.05$), but the intestinal gas discharge time and hospitalization time were significantly shortened in the research group ($P < 0.05$). Further, the research group exhibited significant CEA, CA125, and CA199 reductions after treatment, which were lower compared to the control group, as well as notable increases in TP and TRF that were statistically higher than the control group (all $P < 0.05$). Furthermore, the research group demonstrated an evident decrease in TCM syndrome scores in areas, such as poor appetite, epigastric distension and pain, fatigue and weakness ($P < 0.01$), and abdominal distension after eating, which are notably lower than those in the control group ($P < 0.01$), with a comparable incidence of grades III–IV adverse events ($P > 0.05$).

CONCLUSION

Our research results indicate that Sijunzi decoction plus chemotherapy exerts a good rehabilitation-promoting effect on gastrointestinal function in patients after GC surgery and significantly downregulates abnormally increased CEA, CA125, and CA199 levels.

Key Words: Sijunzi decoction; Chemotherapy; Gastric carcinoma; Gastrointestinal function; Serum markers

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Core Tip: Considering the scarcity of existing research regarding the association of the combination of Sijunzi decoction and chemotherapy with the gastrointestinal function and serum markers of patients after gastric cancer (GC) surgery, this investigation has meticulously conducted a comprehensive, multi-faceted comparative analysis of the clinical efficacy between the therapeutic approach of Sijunzi decoction combined with chemotherapy and chemotherapy alone in such patient populations. The assessment covers a wide array of aspects, including gastrointestinal function, serum markers, nutritional parameters, traditional Chinese medicine syndrome scores, and adverse events. The research results confirmed that the combined Sijunzi decoction and chemotherapy treatment effectively alleviated symptoms, such as poor appetite, epigastric distension and pain, fatigue and weakness, and abdominal distension after eating, besides its remarkable capacity to improve gastrointestinal function, optimize nutritional status, and rectify abnormally increased serum tumor markers in patients after GC surgery. These results will provide novel perspectives and valuable guidance for the clinical management of patients after GC surgery.

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INTRODUCTION

Gastric cancer (GC), a cancer with complex etiologies and heterogeneity, is a crucial primary epithelial malignancy that originates from the stomach[1]. Race, diet, genetic alterations, smoking, alcohol abuse, and *Helicobacter pylori* infection are prevalent pathogenic factors for GC[2]. Global statistics report nearly 1.1 million new GC cases and approximately 800000 deaths annually despite the decline in the incidence and mortality risks of GC[3]. Surgery remains the most crucial and predominantly used approach among the various treatment modalities for GC, including surgery, radiotherapy, chemotherapy, and basic supportive treatment[4,5]. Factors, such as surgical trauma, postoperative complications, and patients' insufficient disease awareness, affect the recovery of gastrointestinal function in patients after GC surgery despite the good efficacy of surgery[6-8]. Hence, the primary emphasis of contemporary research should be firmly focused on exploring innovative therapeutic modalities, with the overarching objective of expediting patient recovery.

Previous evidence has indicated that chemotherapy for patients during GC surgery helps improve the prognosis and survival outcomes of those with resectable gastroesophageal adenocarcinoma[9]. The FOLFOX regimen, consisting of oxaliplatin + calcium folinate + 5-fluorouracil (5-Fu), is a predominant chemotherapy option for patients during GC surgery, with its definite efficacy documented in patients with advanced GC[10,11]. Previous studies have revealed that the FOLFOX regimen plays a pivotal role in augmenting the long-term survival rate of patients diagnosed with localized GC. However, it exerts certain detrimental effects on patients' quality of life. Moreover, it may result in a certain degree of chemotherapy tolerance as well as potential toxic and side effects[12,13]. Sijunzi decoction, a traditional Chinese medicine (TCM) with the effect of invigorating the spleen, can eliminate tumor cells and exert a certain inhibitory effect on tumor metastasis, demonstrating a certain therapeutic potential for tumor diseases[14]. A rat experiment revealed that the use of Sijunzi decoction significantly inhibited the growth of GC side population cells and induced their apoptosis[15]. Moreover, literature has exhibited that Sijunzi decoction plays a certain therapeutic role in intestinal metaplasia of gastric

mucosa, thereby providing a new therapeutic direction for treating precancerous lesions and preventing GC[16].

However, the current research on the effects of Sijunzi decoction combined with chemotherapy on the gastrointestinal function and serum markers of patients after GC remains relatively limited. We believe that analyzing this aspect is beneficial to filling the relevant gaps and expanding the treatment options for such patients.

MATERIALS AND METHODS

General information

This retrospective study included 99 patients with GC who underwent surgery at the Affiliated Hospital of Liaoning University of TCM from June 2022 to February 2024. Patients were categorized into distinct groups based on the variance in treatment regimens. Of them, 45 cases in the control group received chemotherapy (oxaliplatin + calcium folinate + 5-Fu); whereas, 54 cases in the research group were treated with Sijunzi decoction in addition to the treatment administered in the control group. The inclusion of patients in each group is identified with strict adherence to the following inclusion and exclusion criteria to ensure representativeness. Meanwhile, the number of patients in each group is meticulously confirmed to meet the minimum thresholds established through sample size estimation methodologies.

Patient selection criteria

Inclusion criteria: Conforming to the relevant diagnostic criteria specified in the diagnostic criteria for GC[17]; TCM diagnosis: Spleen-qi deficiency diagnosis based on the Guide to Diagnosis and Treatment of Digestive Diseases in TCM [18]; treatment with radical gastrectomy for GC; stages I–III GC without lymph node metastasis; first-time treatment; complete clinical data.

Exclusion criteria: Estimated survival of < 3 months; previous chemoradiotherapy treatment; other malignancies; severe cardiovascular, lung, brain, or kidney dysfunction; immune deficiency; infectious or metabolic disorders; psychological or mental disorders; woman during pregnancy or lactation.

Treatment methods

The control group received the FOLFOX chemotherapy scheme. On the first day, oxaliplatin (130 mg/m^2) was intravenously administered. From day 1 to day 5, an intravenous infusion of 200 mg/m^2 of calcium folinate was administered, followed by an intravenous drip of 5-Fu at 400 mg/m^2. A 21-day period constitutes one treatment course, with a total of four courses administered. The research group was further administered a modified Sijunzi decoction in addition to the above treatment. The prescription consisted of Codonopsis pilosula (30 g), Poria cocos (15 g), Atractylodes macrocephala (15 g), and Radix Glycyrrhizae Preparata (15 g). Astragalus membranaceus at 30 g was added for patients with severe qi deficiency, dried tangerine peel at 12 g and Rhizoma Pinelliae Preparata at 10 g for those with nausea and vomiting, Evodia rutaecarpa at 3 g and Coptis chinensis at 6 g for patients with pantothenic acid and stomach burning sensation, and Radix Aucklandiae at 8 g and Fructus Aurantii at 9 g for patients with qi stagnation. The prescription was given 1 dose/day, which was decocted with water to obtain liquid of 300 mL for administration in the morning and evening (150 mL each time), for 12 weeks. Both groups were treated with antiemesis and vital organ function protection while receiving chemotherapy.

Analysis indexes

(1) Gastrointestinal function: The defecation time, intestinal gas discharge time, and hospitalization time of all patients were documented; (2) Serum markers: Fasting venous blood with a volume of 4 mL was sampled from both patient cohorts and centrifuged to separate the serum for low-temperature preservation and subsequent testing before and after treatment. Enzyme-linked immunosorbent assays (ELISAs) were conducted to identify carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125, and CA199 levels; (3) Nutritional indicators. ELISA was used to detect total protein (TP) and transferrin (TRF) in patients' serum samples; (4) TCM syndrome scores. Changes in TCM syndrome scores before and after treatment were documented, including poor appetite, gastric pain and distension, fatigue and weakness, and abdominal distension after eating. The scores ranged from 0 to 6 points according to the severity of the patient's symptoms, with a total score of 24 points. The more severe the symptom manifestation, the higher the corresponding score; and (5) Safety: Cases with grade III–IV adverse reactions, including gastrointestinal reaction, renal/liver function impairment, and myelosuppression, were observed and recorded, with the incidence rates calculated.

Among the aforementioned indicators, those involving pre- and post-treatment measurements were all assessed before treatment and 12 weeks after treatment initiation.

Statistical analysis

The mean ± SE of the mean was used to statistically describe the quantitative data. The between-group comparisons of measurement data were conducted using independent sample *t*-tests, and pre- and post-treatment comparisons employed paired *t*-tests. Enumeration data were expressed as rates (percentages), and the between-group comparisons adopted χ^2 tests. The obtained experimental data were analyzed by Statistical Package for the Social Sciences version 22.0. A *P* value of < 0.05 indicated statistical significance.

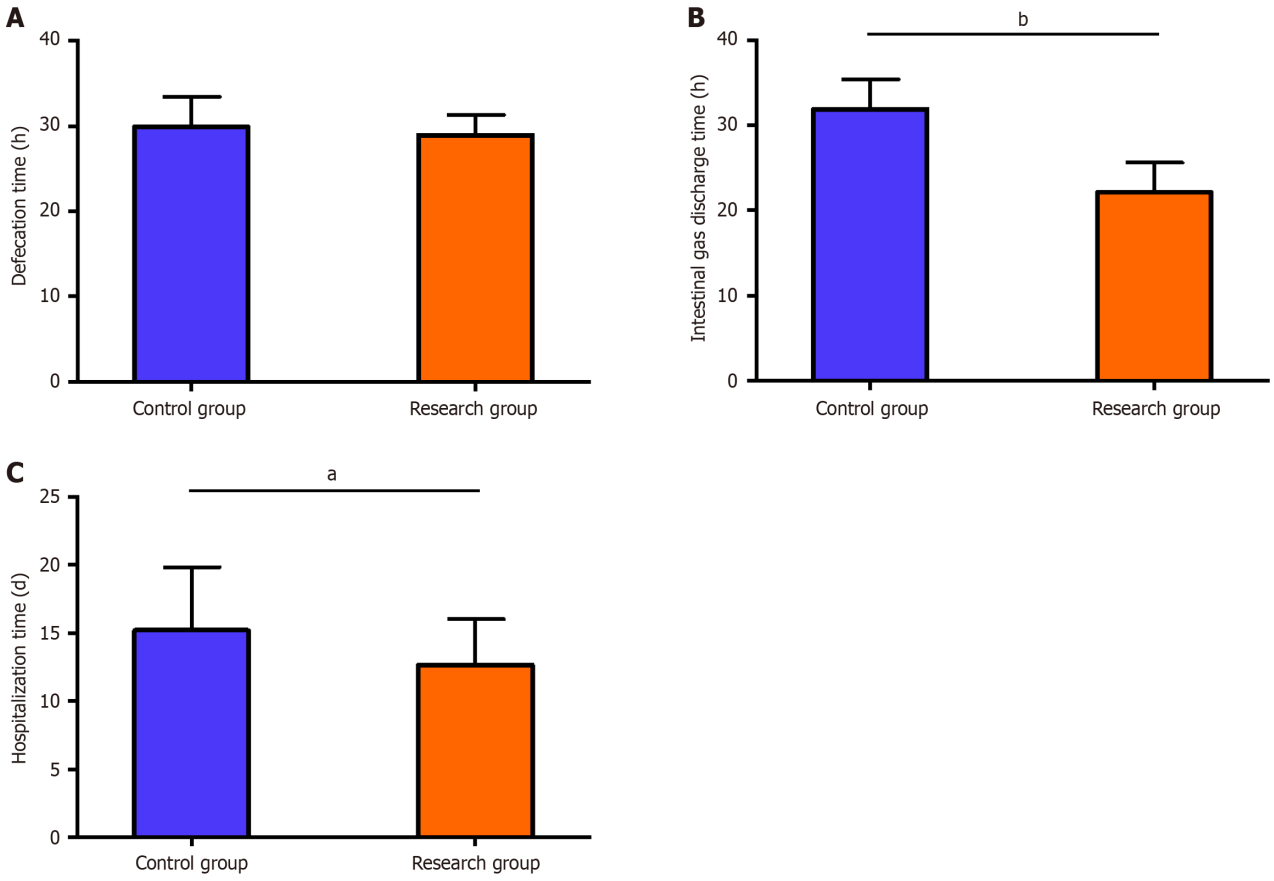


Figure 1 Defecation time, intestinal gas discharge time, and hospitalization time of the two groups. A: Inter-group comparison of defecation time; B: Inter-group comparison of intestinal gas discharge time; C: Inter-group comparison of hospitalization time. $^{a}P < 0.05$, $^{b}P < 0.01$.

RESULTS

Patients' general information

We revealed no evident inter-group differences in terms of age, sex, average body mass, tumor-nodes-metastasis staging, education level, and family history when comparing patients' general information ($P > 0.05$, Table 1).

Gastrointestinal function

The defecation time was 29.87 ± 3.53 hours, the exhaustion time was 31.93 ± 3.46 hours, and the hospitalization time was 15.20 ± 4.62 days in the control group. Conversely, the defecation time was 28.94 ± 2.38 hours, the intestinal gas discharge time was 22.11 ± 3.50 hours, and the length of hospital stay was 12.67 ± 3.36 days in the research group. Comparative analyses revealed comparable defecation time in the control and research groups ($P > 0.05$) but shortened intestinal gas discharge time and hospitalization duration in the research group ($P < 0.05$, Figure 1).

Serum markers

In the control and research groups, the CEA levels were 31.84 ± 3.74 ng/mL and 32.37 ± 3.519 ng/mL before treatment and 17.36 ± 2.89 ng/mL and 11.50 ± 2.73 ng/mL after treatment, the CA125 levels were 59.71 ± 8.52 IU/mL and 62.13 ± 8.49 IU/mL before treatment and 35.02 ± 7.26 IU/mL and 21.61 ± 4.06 IU/mL after treatment, and the CA199 levels were 85.47 ± 6.34 IU/mL and 85.96 ± 6.81 IU/mL before treatment and 27.69 ± 3.18 IU/mL and 17.33 ± 2.77 IU/mL after treatment, respectively. The detection of serum markers, such as CEA, CA125, and CA199, revealed no statistical difference in all these indicators before treatment ($P > 0.05$). Further, all the indexes were significantly inhibited after treatment in the research group ($P < 0.05$), with lower levels than the control group ($P < 0.05$, Figure 2).

Nutritional indicators

The TP levels were 57.62 ± 4.24 g/L and 57.78 ± 4.31 g/L before treatment, which increased to 61.64 ± 4.32 g/L and 66.50 ± 4.73 g/L after treatment in the control and research groups, respectively. The TRF levels were 2.12 ± 0.20 g/L and 2.15 ± 0.23 g/L before treatment, which increased to 2.34 ± 0.39 g/L and 2.87 ± 0.35 g/L after treatment in the control and research groups, respectively. The detection of nutritional indicators, such as TP and TRF, in the two groups revealed similar levels before treatment ($P > 0.05$) and significantly increased levels after treatment ($P < 0.05$). Moreover, the research group demonstrated higher TP and TRF levels than the control group after treatment ($P < 0.05$, Figure 3).

Table 1 Patients' general information

General data	Control group (n = 45)	Research group (n = 54)	χ^2/t	P value
Age (years old)	51.47 ± 6.98	52.59 ± 5.88	0.867	0.388
Sex	29/16	30/24	0.805	0.370
Average body mass (kg)	70.91 ± 5.88	68.67 ± 8.25	1.526	0.130
Tumor-nodes-metastasis staging (I/II/III)	9/24/12	11/25/18	0.607	0.738
Histological classification (poorly differentiated adenocarcinoma/tubular adenocarcinoma/signet-ring cell carcinoma)	22/18/5	25/22/7	0.108	0.948
Education level (below senior high school/senior high school or above)	21/24	18/36	1.828	0.176
Family medical history (none/yes)	37/8	40/14	0.943	0.332

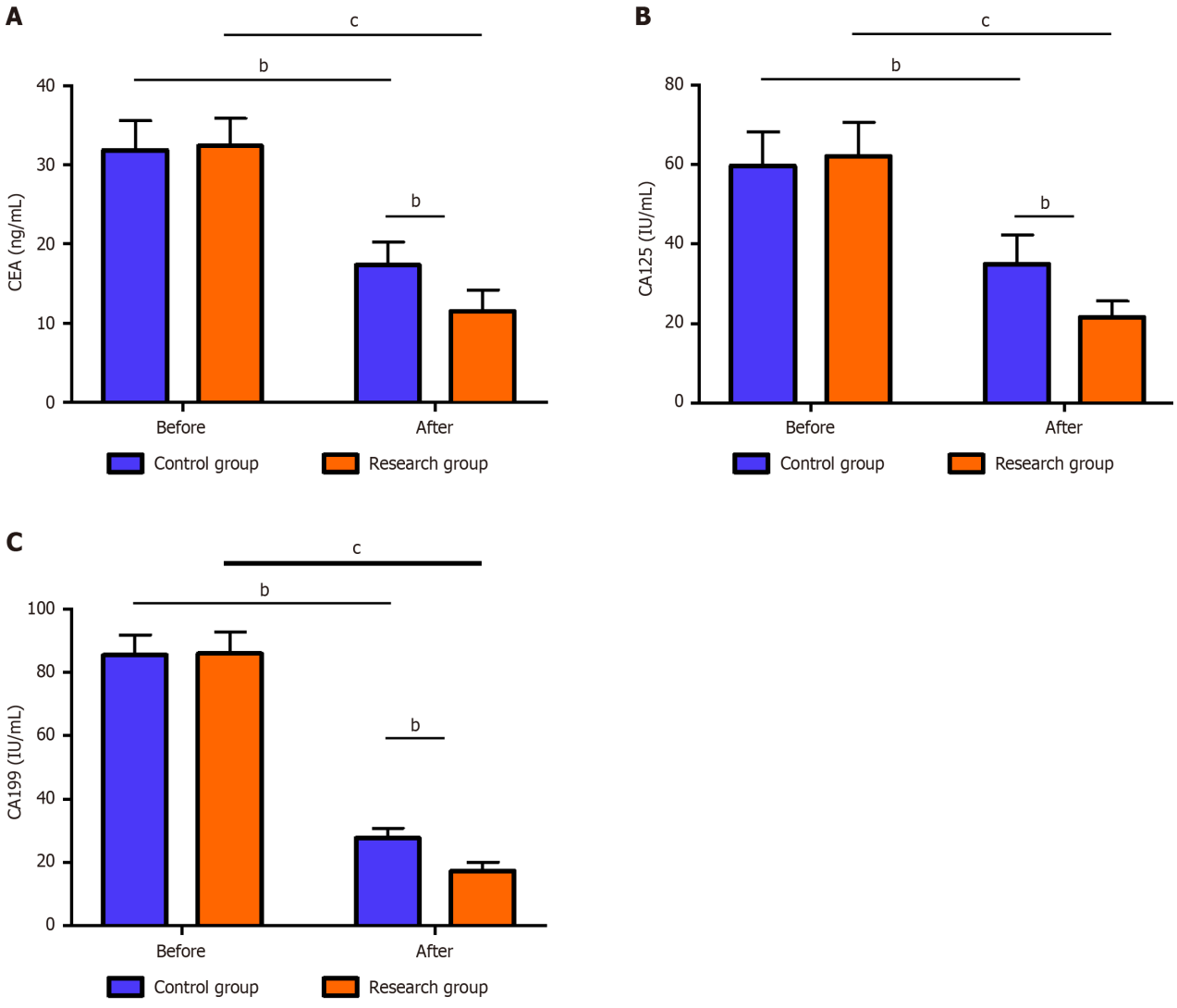


Figure 2 Serum markers of two groups. A: Inter-group comparison of carcinoembryonic antigen levels; B: Inter-group comparison of carbohydrate antigen 125 (CA125) levels; C: Inter-group comparison of CA199 levels. $^{b}P < 0.01$, $^{c}P < 0.001$. CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen.

TCM syndrome scores

Poor appetite scores were 4.49 ± 0.59 points and 4.31 ± 0.58 points before treatment, which decreased to 3.02 ± 0.94 points and 2.11 ± 0.57 points after treatment in the control and research groups, respectively. Epigastric distension and pain scores were 4.42 ± 0.66 points and 4.31 ± 0.67 points before treatment, which decreased to 2.93 ± 0.65 points and, significantly, 1.93 ± 0.64 points after treatment in the control and research groups, respectively. Fatigue and weakness scores were 4.27 ± 0.54 points and 4.07 ± 0.70 before treatment, which decreased to 2.36 ± 0.68 points and 1.70 ± 0.54 points

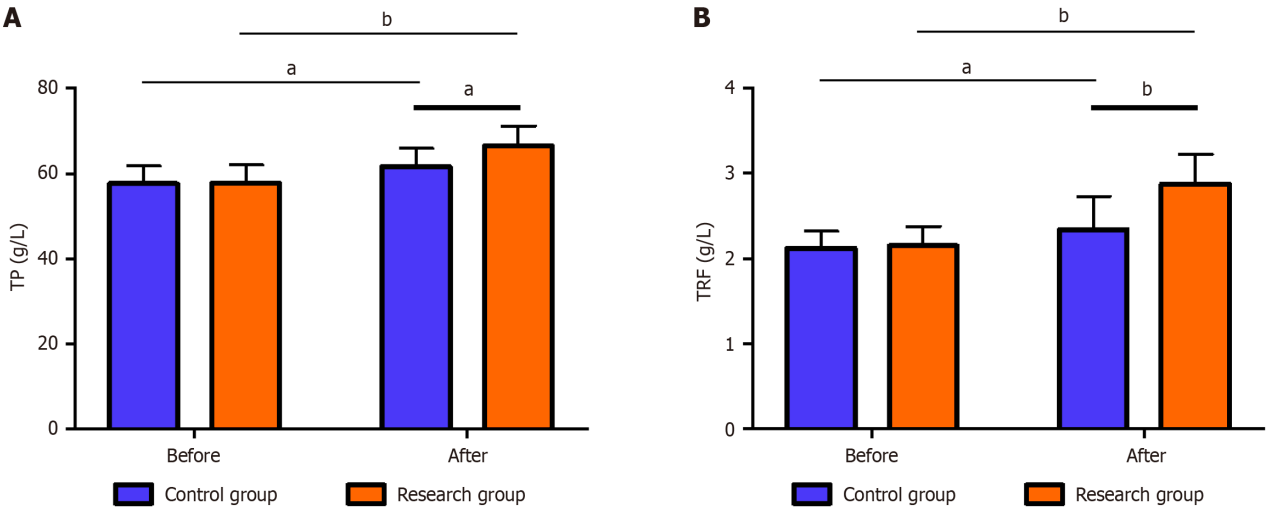


Figure 3 Nutritional indicators. A: Inter-group comparison of total protein levels; B: Inter-group comparison of transferrin levels. $^{a}P < 0.05$, $^{b}P < 0.01$. TP: Total protein; TRF: Transferrin.

after treatment in the control and research groups, respectively. Abdominal distension after eating scores were 4.69 ± 0.51 points and 4.48 ± 0.69 points before treatment, which decreased to 2.89 ± 0.80 points and 2.09 ± 0.81 points after treatment in the control and research groups, respectively. The comparative analysis of pre- and post-treatment TCM syndrome scores in terms of poor appetite, epigastric distension and pain, fatigue and weakness, and abdominal distension after eating revealed no significant difference in each TCM syndrome score between groups before treatment ($P > 0.05$). Further, each TCM syndrome score of both groups was decreased after treatment ($P < 0.05$), particularly in the research group ($P < 0.05$, Figure 4).

Incidence of grade III–IV adverse events in the control and research groups

The incidence rates of grade III-IV adverse events, such as gastrointestinal reactions, renal/liver function impairment, and myelosuppression, indicated comparable incidence rates in the control and research groups ($P > 0.05$, Table 2).

DISCUSSION

Surgical resection is the primary treatment method for patients with GC. However, it may cause postoperative gastrointestinal dysfunction, mainly manifested as weakened gastrointestinal peristalsis and consequently the gradual gastrointestinal secretion accumulation[19]. This does not only induce nutritional deficiency in patients with GC but may also cause systemic dysfunction, affecting normal postoperative recovery[20,21]. Thus, exploring an effective treatment method that is beneficial for the recovery of gastrointestinal function in patients after GC surgery is extremely important.

The theory of TCM indicates that patients after GC surgery present manifestations, such as blood and qi deficiency and spleen and stomach weakness, which may further result in insufficiency of the body's vital qi[22]. Sijunzi decoction is composed of Radix Codonopsis, Poria cocos, Rhizoma Atractylodis Macrocephalae, Radix Glycyrrhizae Preparata, *etc.* Codonopsis pilosula benefits qi, harmonizes the stomach, strengthens the spleen, and dries dampness. Poria cocos and Rhizoma Atractylodis Macrocephalae are conducive to restoring the function of transporting spleen-qi and oozing dampness and turbidity out of the body. Radix Glycyrrhizae Preparata exerts effects of invigorating qi, tonifying the spleen, and harmonizing various medicines. The above medicines work together to exhibit the role of reinforcing the spleen and invigorating the stomach. The dosage of Astragalus membranaceus is increased in patients with severe qi deficiency to maximize therapeutic effectiveness[23-26]. Previously, several studies have conducted in-depth analyses of the therapeutic mechanism of Sijunzi decoction. Ding *et al*[27] emphasized that the therapeutic mechanism of Sijunzi decoction in GC may be associated with its effects of vascular proliferation inhibition and phosphoinositol-3-kinase/protein kinase B pathway regulation to induce apoptosis. Li *et al*[28] revealed that the anti-GC therapeutic effect of Sijunzi decoction is associated with its suppression effects on β-catenin nuclear accumulation and DNA binding activity. In this study, the research group demonstrated shorter defecation time than the control group, but the difference was not significant. However, the intestinal gas discharge time and hospitalization time were significantly shorter in the research group than in the control group, indicating that the combination of Sijunzi decoction and chemotherapy is somewhat beneficial for gastrointestinal function and postoperative recovery improvement in patients after GC surgery. This could be because the herbal components of Sijunzi decoction can ameliorate the spleen-deficiency syndrome in patients. They achieve this by alleviating diarrhea, rectifying gastrointestinal hormone and neurotransmitter secretion disorders, and mending ileal morphology and intestinal barrier damage[29]. The measurement of nutritional indicators revealed statistically increased TP and TRF after treatment in the research group, which was notably higher than in the control group, indicating that Sijunzi decoction plus chemotherapy in patients after GC surgery could significantly improve the

Table 2 Incidence of grade III-IV adverse events, *n* (%)

General data	Control group (*n* = 45)	Research group (*n* = 54)	χ^2	*P* value
Gastrointestinal reaction	4 (8.89)	3 (5.56)		
Renal function impairment	2 (4.44)	2 (3.70)		
Liver function impairment	2 (4.44)	1 (1.85)		
Myelosuppression	1 (2.22)	1 (1.85)		
Total	9 (20.00)	7 (12.96)	0.897	0.344

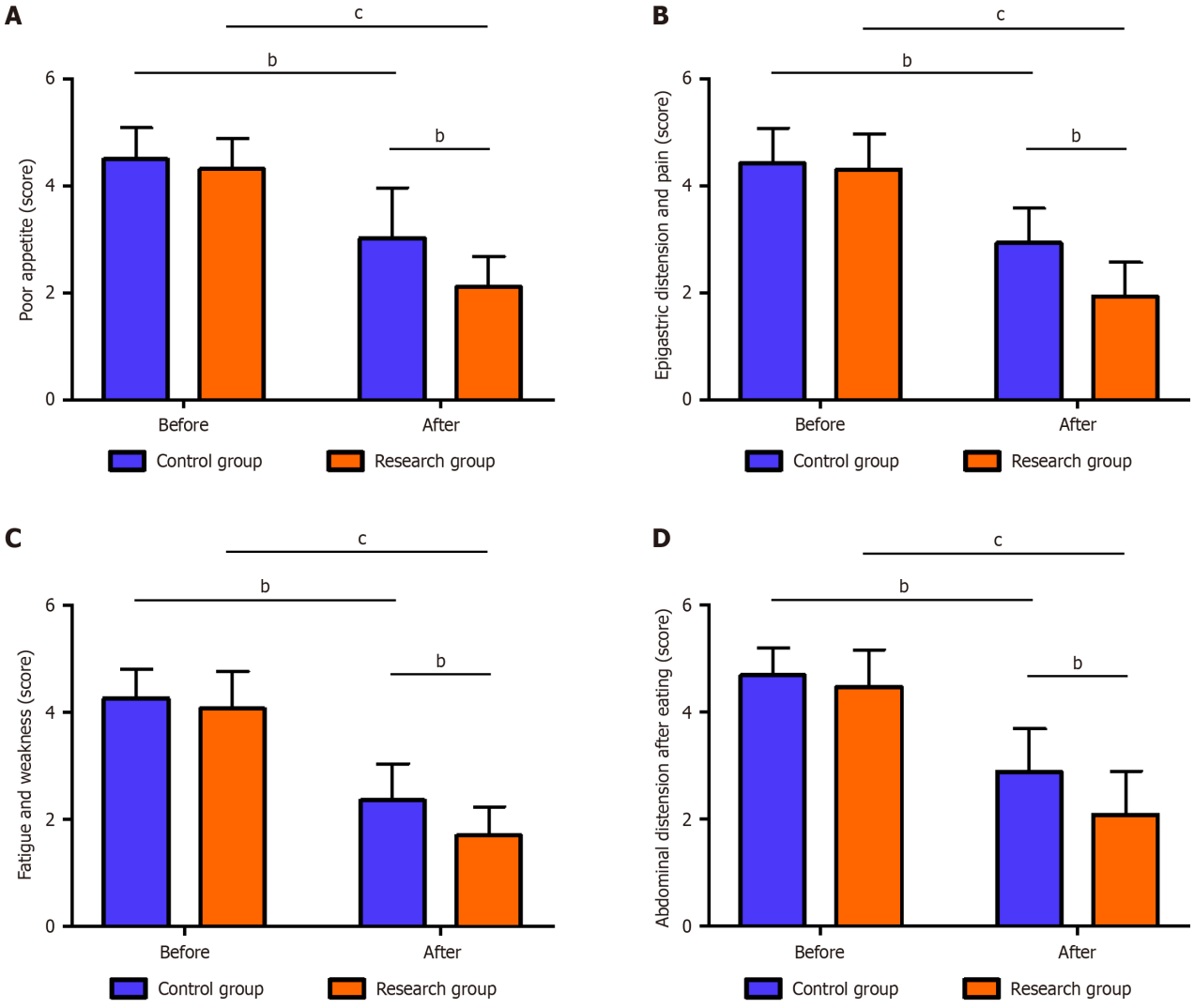


Figure 4 Traditional Chinese medicine syndrome scores. A: Poor appetite scores before and after treatment in the two groups; B: Epigastric distension and pain scores before and after treatment in the two groups; C: Fatigue and weakness scores of the two groups before and after treatment; D: Abdominal distension after eating scores before and after treatment in the two groups. $^{b}P < 0.01$, $^{c}P < 0.001$.

nutritional status. The above-mentioned effects may be attributed to various components utilized in the Sijunzi decoction. Once harmonized, they synergistically perform functions such as strengthening the spleen, benefiting the stomach, replenishing qi, and nourishing blood. Additionally, they improve the gastrointestinal function of patients with GC and enhance the body's nutritional status by regulating the composition and proportion of the gut microbiota[30]. Serum tumor markers, including CEA, CA125, and CA199, were markedly decreased after treatment in the research group, which were statistically lower than the control group, indicating that the combination of Sijunzi decoction and chemotherapy intervention actively regulates abnormal CEA, CA125, and CA199 levels in patients after GC surgery. Moreover, the down-regulation of the aforementioned serum tumor markers in patients with GC caused by Sijunzi decoction may be attributed to its potential regulatory effect on exosomal microRNA-151-3p in saliva[31]. The investigation of TCM syndrome scores revealed greatly reduced scores of the research group in terms of poor appetite, gastric pain and distension, fatigue and weakness, and abdominal distension after eating after treatment, which were si-

gnificantly lower than those of the control group. This indicates that receiving the combination of Sijunzi decoction and chemotherapy treatment for patients after GC surgery significantly alleviates typical clinical symptoms. As far as safety is concerned, the total incidence rates of grade III–IV adverse events, such as gastrointestinal reactions, renal/liver function impairment, and myelosuppression, in the research group was comparable to that in the control group (12.96% *vs* 20.00%). This indicates that the combination of Sijunzi decoction and chemotherapy does not remarkably augment the risk of adverse events in patients after GC surgery. A meta-analysis reveals that Sijunzi decoction significantly shortens flatulence and hospitalization duration, reduces postoperative complication incidences, and increases albumin, prealbumin, and TRF levels in patients with GC, similar to our research results[32]. A prospective observational cohort study demonstrated that Sijunzi decoction for patients postoperatively with non-small cell lung cancer significantly alleviated specific symptoms, such as dyspnea, cough, hemoptysis, pain, and peripheral neuropathy, thereby supporting our research results[33].

This research has several limitations. First, considering its retrospective design, the implementation of a prospective study in the future would, to a certain extent, be instrumental in circumventing issues related to information collection bias. Second, the sample size needs to be increased. Conducting a multi-center, large-scale sample analysis in the future will be conducive to improving the accuracy of the research results. Third, the inclusion of additional sampling time points would make the dynamic alteration analysis in diverse data of patients throughout the entire treatment course possible. In the future, a thorough analysis aimed at the improvement of this research project will be executed from the aspects expounded above.

CONCLUSION

Altogether, the combination of the Sijunzi decoction and chemotherapy exerts a positive effect on improving the gastrointestinal function and nutritional status of patients after GC surgery. It significantly downregulates serum tumor marker levels, such as CEA, CA125, and CA199, and alleviates symptoms, including poor appetite, gastric pain and distension, fatigue and weakness, and postprandial abdominal distension, while ensuring a favorable clinical safety profile. The aforementioned results provide effective intervention options for the perioperative intervention of patients after GC surgery and offer more references and evidence for the clinical management of such patients.

FOOTNOTES

Author contributions: Wang XD and Su XQ designed the study, collected and analyzed data, and wrote the manuscript; Wang XD and Su XQ participated in the study's conception and data collection; Wang XD, Su XQ and Gao H participated in study design and provided guidance. All authors read and approved the final version. Wang XD and Su XQ contributed equally to this work as co-first authors.

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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

Effects of *Bifidobacterium* triple viable bacteria-assisted mirtazapine in managing depression in patients after radical surgery for gastric cancer

Heng Lu, Wei-Dong Wu, Li Ji, Xiao-Yan Xu

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Abstract

BACKGROUND

Patients with gastric cancer may have a risk of depression after radical surgery, which affects recovery and requires intensive intervention.

AIM

To explore the role of *Bifidobacterium* triple viable bacteria-assisted mirtazapine in patients with depression after radical surgery for gastric cancer.

METHODS

This study included 80 patients with gastric cancer who experienced depression after undergoing radical surgery from January 2022 to December 2023 at Jiangnan University Hospital in Wuxi city in Jiangsu province. The patients were categorized into the control group (n = 40) treated with mirtazapine and observation group (n = 40) treated with combined *Bifidobacterium* triple viable bacteria-assisted mirtazapine. Neuroendocrine index, intestinal flora level, nutrition status, and patient quality of life were analyzed.

RESULTS

Before drug index level, no statistically significant difference was observed

between the two groups $P > 0.05$). After drug administration, both groups experienced a decline in depression scores, cortisol, *Escherichia coli*, *Enterococcus faecalis* levels, and quality of life scores, whereas dopamine, serotonin, *Lactobacillus*, *Bifidobacteria*, hemoglobin, serum albumin and prealbumin levels increased. The observation group demonstrated significantly greater improvements across these indicators, with significant differences within groups and between groups ($P < 0.05$).

CONCLUSION

Bifidobacterium has a relieving effect on depression in patients after radical surgery for gastric cancer, improves neuroendocrine status, regulates intestinal flora, and improves nutritional status and quality of life.

Key Words: *Bifidobacterium* triple bacteria; Oryzazapine; Radical gastric cancer; Depression; Neuroendocrine; Intestinal flora; Quality of life

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Core Tip: Post-gastric cancer radical surgery, patients are susceptible to depression, impacting recovery and quality of life. It's vital to screen for depressive symptoms promptly. Tailored interventions, including targeted medication to regulate gut microbiota, can alleviate depression and enhance prognosis. Integrating these with psychological support and lifestyle modifications, such as a balanced diet and regular physical activity, can further improve mental health and foster better adaptation post-surgery. A holistic approach ensures patients receive comprehensive care, optimizing their recovery journey and well-being.

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INTRODUCTION

Gastric cancer is a malignancy of the digestive tract that originates in the gastric epithelial cells. Although its exact cause is not fully understood, it is associated with *Helicobacter pylori* infection, genetic factors, and unhealthy habits. A history of gastric disease can also increase the risk of occurrence. Patients often experience anorexia, nausea, and indigestion. As the tumor enlarges, it invades the surrounding organs, leading to complications and potentially life threatening consequences [1]. The incidence and mortality rates of this disease are high. Clinically, radical surgery is commonly performed to remove primary lesions, affected tissues, and regional lymph nodes, aiming to eradicate the cancer and minimize residual risk. However, surgery acts as a major stressor, potentially affecting the psychological state of patients. This, coupled with the impact of postoperative chemotherapy, its associated adverse reactions, and financial burden, can increase psychological pressure on patients and lead to postoperative depression. Depression, in turn, can lead to physical symptoms, aggravating the original condition and forming a vicious circle that ultimately decreases the quality of life[2]. Therefore, it is necessary to pay attention to the antidepressant treatment of patients with malignant tumors to maintain a healthy attitude and ensure treatment efficacy. Mirtazapine, an antidepressant, is well-tolerated and has no effect on the cardiovascular system. However, this drug can only help patients relieve their depressive symptoms but does not address intestinal flora disorders and malnutrition caused by the disease. Therefore, a combination drug regimen is necessary[3]. *Bifidobacterium* triplex, composed of multiple bacteria, is effective in treating diarrhea, constipation, and indigestion caused by intestinal dysbiosis[4]. This study explores the roles and effectiveness of combination regimens in managing depression in patients after radical surgery for gastric cancer.

MATERIALS AND METHODS

General information

In total, 180 patients with depression after radical surgery were admitted to the Department of Gastrointestinal Surgery at Jiangnan University, Wuxi, Jiangsu Province, China. The treatment was performed from January 2022 to December 2023, and the patients were categorized into the control ($n = 4$) and observation ($n = 4$) groups according to the medications prescribed. The inclusion criteria were as follows: (1) All gastric cancer diagnosis, confirmed through surgical pathological examinations; (2) Radical resection of gastric cancer and postoperative depression; (3) Age > 30 years; (4) No previous history of drug allergy; and (5) Good data support for the study. The exclusion criteria were as follows: (1) Organic lesions; (2) Other malignancies; (3) A previous psychiatric history; and (4) Treatment performed within 2 weeks.

The specific recruitment process was as follows: (1) Preliminary screening: We initially conducted a preliminary screening of all patients who underwent radical surgery in the Department of Gastrointestinal Surgery, examining their medical records to determine whether they met the inclusion criteria, such as age range and type of surgery, among other basic conditions; (2) Symptom assessment: For patients who met the inclusion criteria, professional psychiatrists used validated depression assessment scales (such as the Hamilton Depression Rating Scale) to conduct a detailed evaluation, accurately determining whether they had depression and ensuring that all included patients were diagnosed with depression; (3) Exclusion of ineligible individuals: During assessment, we strictly adhered to the exclusion criteria, excluding patients with severe cognitive impairment, a history of other psychiatric disorders such as schizophrenia, or those taking medications that might affect the study results to ensure the homogeneity of the study participants and the reliability of the research findings; and (4) Final determination: After rigorous selection, 180 patients with depression following radical surgery who met the inclusion criteria were included in this study.

Methods

For the control group, mirtazapine tablets (Shanxi Kangbao Biological Products Co., Ltd., Changzhi, China; approval number: Sinopharm approved H20080101; specification: 15 mg) were administered orally once a day, with one tablet taken per day initially, which was adjusted to 30 mg per day after 1 week. This regimen was continued for 8 weeks. For the observation group, in addition to mirtazapine, *Bifidobacterium* triple viable bacteria capsules (Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd., Shanghai, China; approval number: S10950032; specification: 0.21 g) was administered orally, with 204 capsules taken twice a day and continued for 8 weeks. The dosage of mirtazapine was based on preclinical studies and data from previous clinical trials, ensuring optimal therapeutic effects within the effective dosage range. The dosage of *Bifidobacterium* triple viable bacteria was determined by referring to previous research and clinical application experience, ensuring its efficacy in modulating the gut microbiota and improving neuroendocrine status, while also ensuring patient tolerability.

Observational indicators

Depressive symptoms: These were assessed using the Zung's Self-Rating Depression Scale (SDS)[5], Hamilton Depression Scale (HAMD), and Beck Depression Scale [Back Depression Inventory (BDI)][6]. The SDS comprises 20 items, each scored from 0 to 4. Scale score of 1.25 is the actual score. A score below 50 indicates normal mood, 50-59 indicates mild depression, 60-69 indicates moderate depression, and ≥ 70 indicates severe depression. The HAMD scale includes 17 items, with a total score of ≤ 7 indicating no depression, 8-17 indicating mild depression, 18-24 indicating moderate depression, ≥ 25 indicating severe depression. The BDI scale includes 13 items, each scored from 0 to 3, with a total score of 39. A score of 4 is suggestive of the absence of depression, while those of 5-7, 8-15, and 16 indicate mild, moderate and severe depression, respectively.

Neuroendocrine status: To assess this, 5 mL of fasting venous blood was drawn before and after 2 months of treatment. Blood samples were centrifuged at 3500 rpm for 5 minutes using a medical centrifuge (Jiangsu Xinkang Medical Instrument Co., Ltd., Taizhou, China, record number: 20180077, model and specification: 80-3B). The radi and time lengths were 10 cm and 5 min, respectively. The upper layer of the serum was collected using a fully automatic biochemical analyzer (Dirui Medical Technology Co., Ltd., Changchun, China, registration certificate number: 20192220209, model specification: CS-1600A). Dopamine, serotonin, and cortisol levels were measured using enzyme-linked immunosorbent assay.

Intestinal flora: Fresh stool samples (0.1 g) were collected from both groups before and after treatment. Samples were diluted in normal saline and cultured on a media, suitable for anaerobic and aerobic bacteria, at 37 °C for 48-72 hours. A semi-automatic biological identification instrument (Shandong Xinke Biological Technology Co., Ltd., Beijing, China, registration number: Lu Xie injection 20172220068, model specification: XK-3401) was used to calculate the colony counts of *Lactobacillus*, *Bifidobacterium*, *Escherichia coli* (*E. coli*), and *Enterococcus faecium* (*E. faecalis*).

Nutritional status: Fasting venous blood sample was collected as described above, and the levels of hemoglobin (colorimetric method), serum albumin (bromide cresyl green method), and prealbumin levels were measured using the automatic biochemical analyzer.

Quality of life: This was assessed using the European Organization for Cancer Research and Treatment of the Core Scale of Life Gastric Cancer Scale[7]. The scale includes 22 items, each scored between 1 and 4, with subscales for dysphagia (4, 16 points), stomach pain (4, 16 points), restricted diet (4, 16 points), hiccups (3, 12 points), anxiety (3, 12 points), single-item measures (4, 16 points). The total score is 88, a reduction in scores indicate improved quality of life.

Statistical analysis

Data were analyzed using SPSS (version 22.0; IBM, Armonk, NY, United States). Count data are represented as percentages (%) and analyzed using the χ^2-test. Upon examination, the expected frequencies in all cells were greater than 5, and the sample data were independent of each other, satisfying the assumptions of the χ^2-test and, thereby, ensuring the validity of the test results. Data with normal distribution are expressed as mean ± SD and analyzed using the *t*-test. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Basic data of the study subjects

In total, 180 patients with depression after radical surgery were admitted to the Department of Gastrointestinal Surgery at Jiangnan University, Wuxi, Jiangsu Province, China. The treatment was performed from January 2022 to December 2023, and the patients were categorized into the control and observation groups according to the medications prescribed. The inclusion criteria were as follows: (1) A diagnosis of gastric cancer, confirmed through surgical pathological examinations; (2) Radical resection of gastric cancer and postoperative depression; (3) Age > 30 years; (4) No previous history of drug allergy; and (5) Reliable data support for the study. The exclusion criteria were as follows: (1) Organic lesions; (2) Other malignancies; (3) A previous psychiatric history; and (4) Treatment performed within 2 weeks.

Depression

The premedication scores were comparable between the two groups ($P > 0.05$). Following treatment, the SDS, HAMD, and BDI scores were lower in the observation group than in the control group. Differences were significant both between and within the groups ($P < 0.05$) (Table 1).

Neuroendocrine index

Before treatment, no significant difference in dopamine, serotonin, and cortisol levels was observed between the two groups ($P > 0.05$). After treatment, dopamine and serotonin levels increased, whereas cortisol levels decreased, with significant differences between and within the groups ($P < 0.05$) (Table 2).

Intestinal microbiota levels

Premedication levels of intestinal flora were comparable between the groups ($P > 0.05$). After treatment, the colony counts of *Lactobacillus* and *Bifidobacterium* increased, whereas those of *E. coli* and *E. faecalis* decreased in both groups. The observation group demonstrated a more significant change than the control group. Differences between the groups were statistically significant ($P < 0.05$) (Table 3).

Nutritional status

Before treatment, no significant difference in hemoglobin, serum albumin, and prealbumin levels was observed between the two groups ($P > 0.05$). After treatment, hemoglobin, serum albumin, and prealbumin levels increased, with the observation group showing significantly greater improvement than the control group. Differences were significant between and within the groups ($P < 0.05$) (Table 4).

Quality of life

No significant difference in premedication scores was observed between the two groups ($P > 0.05$). After treatment, the scores in both groups improved, with greater reductions in symptom dimensions and total scores in the observation group than in the control group. Differences were significant between and within the groups ($P < 0.05$) (Table 5).

DISCUSSION

Radical gastrectomy for gastric cancer is a curative procedure that involves simultaneous removal of the primary tumor, metastatic lymph nodes, and infiltrated tissues, ensuring that no residual cancer remains. This approach aims to cure the disease and reduce the risk of recurrence. Malignant tumors can cause physical discomfort and mental illness in patients. Postoperative depression, a common emotional pathological reaction, adversely affects patients' mental health, delays postoperative recovery, and reduces the quality of life. Mirtazapine is a widely used antidepressant that acts against the central presynaptic membrane α-2 receptor and stimulates adrenergic nerve conduction. It can block the central serotonin receptor, with its enantiomers. Additionally, it has antihistamine receptor, offering sedative effects, good tolerance, no anticholinergic effect, and no cardiovascular risks[8]. *Bifidobacterium* triads for probiotics comprises long *Bifidobacterium*, *Lactobacillus acidophilus*, and *E. faecalis*. These probiotics can grow under different conditions and can work promptly and persistently after oral intake. They colonize the intestinal mucosal to form a biological barrier, inhibit the proliferation of pathogenic bacteria, reduce the risk of pathogenic infections, and maintain the balance of intestinal flora, thereby supporting physiological functions[9].

Gut flora dysbiosis is closely related to the development of mental disorders, which can be mediated through neurotransmitters or immune responses in the central nervous system, thus affecting human behavior. The intestinal flora actively participates in the interaction with the brain and can assist in the treatment of depression. The findings of this study showed that the observation group had significantly lower depression scores than the control group ($P < 0.05$), indicating the antidepressant efficacy of *Bifidobacteria* triple viable bacteria. This compound preparation supplements beneficial bacteria, inhibits harmful bacteria, and restores intestinal flora balance. It can also inhibit the continuous activation of the hypothalamic-pituitary-adrenal axis and enhance the antidepressant effect of mirtazapine.

Emotional and behavioral regulation is closely related to neuroendocrine states. Neuroendocrine disorders can reduce the ability to control emotions and behaviors in patients, leading to mental disorders. Compared to the control group, the observation group had higher dopamine and serotonin levels and lower cortisol levels ($P < 0.05$), suggesting that the adjuvant use of *Bifidobacterium* triple viable bacteria could regulate the neuroendocrine state of the body. This drug acts

Table 1 Depressed mood scores, mean ± SD

Group	Case	Before, SDS	After, SDS	Before, HAMD	After, HAMD	Before, BDI	After, BDI
Control	40	65.44 ± 3.18	53.27 ± 2.45[a]	21.16 ± 2.24	10.14 ± 2.12[a]	13.16 ± 1.24	6.12 ± 0.78[a]
Observation	40	65.72 ± 3.32	48.12 ± 2.96[a]	21.27 ± 2.12	6.36 ± 1.18[a]	13.20 ± 1.21	3.21 ± 0.54[a]
t		0.385	8.477	0.226	9.853	0.146	19.400
P value		0.701	< 0.001	0.822	< 0.001	0.884	< 0.001

[a]*P* < 0.05. Comparison within the group before treatment.
SDS: Self-Rating Depression Scale; HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory.

Table 2 Neuroendocrine indicators, mean ± SD

Group	Case	Before, dopamine (pg/mL)	After, dopamine (pg/mL)	Before, 5-hydroxytryptamine (pg/mL)	After, 5-hydroxytryptamine (pg/mL)	Before, hydrocortisone (ng/mL)	After, hydrocortisone (ng/mL)
Control	40	40.12 ± 10.45	55.16 ± 12.24[a]	159.28 ± 40.18	182.15 ± 42.44[a]	212.72 ± 60.24	160.45 ± 31.78[a]
Observation	40	40.27 ± 10.32	76.18 ± 13.21[a]	160.12 ± 41.45	221.36 ± 45.52[a]	214.56 ± 62.48	121.54 ± 24.62[a]
t		0.065	7.382	0.092	3.985	0.134	6.121
P value		0.949	< 0.001	0.927	< 0.001	0.894	< 0.001

[a]*P* < 0.05. Comparison within the group before treatment.

Table 3 Levels of the intestinal microbiota, mean ± SD, CFU/g

Group	Case	Before, *Lactobacillus acidophilus*	After, *Lactobacillus acidophilus*	Before, *Bifidocaterium*	After, *Bifidocaterium*	Before, *Escherichia coli*	After, *Escherichia coli*	Before, *Enterococcus faecalis*	After, *Enterococcus faecalis*
Control	40	6.32 ± 0.56	6.92 ± 0.48[a]	7.54 ± 0.52	8.21 ± 0.44[a]	10.27 ± 1.18	8.72 ± 0.80[a]	8.18 ± 0.82	7.12 ± 0.68[a]
Observation	40	6.35 ± 0.52	7.54 ± 0.42[a]	7.48 ± 0.56	9.12 ± 0.42[a]	10.21 ± 1.24	7.32 ± 0.64[a]	8.21 ± 0.78	6.08 ± 0.54[a]
t		0.248	6.148	0.497	9.462	0.222	8.643	0.168	7.575
P value		0.805	< 0.001	0.621	< 0.001	0.825	< 0.001	0.867	< 0.001

[a]*P* < 0.05. Comparison within the group before treatment.

Table 4 Nutritional status, mean ± SD

Group	Case	Before, hemoglobin (g/L)	After, hemoglobin (g/L)	Before, blood albumin (g/L)	After, blood albumin (g/L)	Before, prealbumin (mg/L)	After, prealbumin (mg/L)
Control	40	90.12 ± 8.16	99.18 ± 6.32[a]	28.27 ± 3.42	32.12 ± 3.56[a]	245.72 ± 14.18	272.15 ± 10.44[a]
Observation	40	89.72 ± 8.24	110.24 ± 5.72[a]	28.14 ± 3.68	36.21 ± 3.12[a]	246.32 ± 12.56	298.42 ± 14.28[a]
t		0.218	8.206	0.164	5.465	0.200	9.392
P value		0.828	< 0.001	0.870	< 0.001	0.842	< 0.001

[a]*P* < 0.05. Comparison within the group before treatment.

Table 5 Quality of life, mean ± SD

Group	Control	Observation	*t*	*P* value
Case	40	40		
Before, dysphagia	11.12 ± 1.48	11.32 ± 1.56	0.588	0.558
After, dysphagia	8.24 ± 1.36[a]	6.16 ± 1.12[a]	7.467	< 0.001
Before, stomach pain	10.78 ± 1.24	10.86 ± 1.20	0.293	0.770
After, stomach pain	8.12 ± 1.18[a]	6.24 ± 0.96[a]	7.816	< 0.001
Before, dietary restriction	10.84 ± 1.16	10.78 ± 1.12	0.235	0.815
After, dietary restriction	8.20 ± 1.32[a]	6.54 ± 1.18[a]	5.930	< 0.001
Before, hiccups	8.72 ± 1.16	8.78 ± 1.20	0.227	0.821
After, hiccups	7.08 ± 0.72[a]	5.80 ± 0.64[a]	8.404	< 0.001
Before, anxiety	8.12 ± 1.18	8.16 ± 1.12	0.155	0.877
After, anxiety	6.72 ± 0.78[a]	5.24 ± 0.42[a]	10.566	< 0.001
Before, single entry	10.16 ± 1.24	10.12 ± 1.28	0.142	0.887
After, single entry	8.20 ± 1.12[a]	6.44 ± 1.10[a]	7.091	< 0.001
Before, total score	59.74 ± 7.46	60.02 ± 7.48	0.168	0.867
After, total score	46.56 ± 6.48[a]	36.42 ± 5.42[a]	7.591	< 0.001

[a]$P < 0.05$. Comparison within the group before treatment.

on the central nervous system, protects neurons in the brain, inhibits synaptic changes, regulates neuroendocrine indicators, and controls disease progression.

Patients with digestive system diseases often experience intestinal flora disorders, characterized by a decrease in the colony counts of beneficial bacteria and an increase in those of harmful bacteria. Postoperative intestinal flora imbalances not only compromise surgical outcomes but also increase the severity of postoperative depression. Compared to the control group, the observation group had significantly higher colony counts of *Lactobacillus* and *Bifidobacterium* and lower colony counts of *E. coli* and *E. faecalis* ($P < 0.05$), indicating that *Bifidobacterium* can regulate and stabilize the intestinal flora. After oral administration, *Bifidobacterium* triple viable bacteria colonize the intestinal tract and inhibits the invasion of pathogenic bacteria. In addition, these probiotics can adjust oxygen concentrations within the gut, fostering an environment conducive to the growth of beneficial bacteria while suppressing harmful pathogens[10].

In this study, the nutritional status of the two groups was further compared, and the results showed that the level of each indicator was higher in the observation group than in the control group ($P < 0.05$), confirming that the *Bifidobacterium* triad can improve the nutritional status of patients. The maltodextrin and sugarcane fruit oligosaccharides in the drug formulation create favorable conditions for the colonization of beneficial bacteria and promote the repair of the damaged mucosal barrier. Additionally, the polysaccharides in the drug can stimulate the intestinal tract, promote its peristalsis, improve gastrointestinal function, improve the body's ability to absorb nutrients, supplement the normal physiological bacteria, inhibit and remove pathogenic bacteria, reduce endotoxin, enhance the body's ability to digest and absorb nutrients, and improve the nutritional status. Compared with the control group, the observation group had a lower quality of life score ($P < 0.05$), indicating that the adjuvant use of the *Bifidobacteria* triad improves patients' quality of life. The combined therapy with mirtazapine and *Bifidobacterium* triple viable bacteria can alleviate physical symptoms and mental disorders, relieve indigestion symptoms, reduce stomach discomfort, help patients to return to a normal diet, reduce psychological pressure, reduce negative emotional influence, maintain good physiological and psychological state, and improve the quality of life.

Numerous studies have shown that mirtazapine monotherapy can effectively alleviate depressive symptoms, but its regulatory effects on neuroendocrine status and the gut microbiota are limited. In this study, the combination of *Bifidobacterium* triple viable bacteria and mirtazapine significantly relieved depressive symptoms and improved the neuroendocrine status and the gut microbiota, demonstrating a more comprehensive therapeutic effect than that of mirtazapine alone[11]. To our knowledge, this is the first study to explore the multi-target therapeutic mechanisms of *Bifidobacterium* triple viable bacteria combined with mirtazapine in managing depression in patients after radical gastrectomy for gastric cancer. This combination therapy alleviated depressive symptoms, improved neuroendocrine status and restored the gut microbiota, providing new insights for the comprehensive treatment of postoperative depression. *Bifidobacterium* triple viable bacteria combined with mirtazapine can effectively alleviate postoperative depressive symptoms in patients after radical gastrectomy for gastric cancer, helping patients cope better with postoperative psychological stress and promoting psychological recovery. This combination has the potential to become an effective treatment option, providing comprehensive support for the postoperative recovery of patients. Although short-term studies have shown that the combination of mirtazapine and *Bifidobacterium* triple viable bacteria is significantly effective, further research is needed to investigate

its long-term effects. The potential for drug resistance or other complications associated with prolonged use requires continuous monitoring in clinical practice.

CONCLUSION

Bifidobacterium triple viable bacteria combined with mirtazapine can relieve depression after radical surgery for gastric cancer, regulate both neuroendocrine and intestinal flora disorders, and improve nutritional status and patient's quality of life.

FOOTNOTES

Author contributions: Lu H designed the study; Lu H, Xu XY, Wu WD, and Ji L contributed to the analysis of the manuscript, the data collection and writing of this article; and all the authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of the effect of multi-channel continuous nursing intervention on patients post-radical gastrectomy

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Abstract

BACKGROUND

Radical gastrectomy (RGE) for gastric carcinoma (GC) has exerted definite therapeutic efficacy in treating patients with GC. However, a notable risk of post-operative complications (POCs) persists among middle-aged and elderly patients with compromised physiological functions. Hence, developing and implementing reliable nursing interventions to optimize the comprehensive management of these patients is deemed imperative.

AIM

To analyze the association of multi-channel continuous nursing intervention with POCs, negative emotions (NEs), and quality of life (QoL) of patients undergoing RGE for GC.

METHODS

This retrospective study selected 99 patients who underwent RGE for GC in our hospital from May 2020 to May 2023. Participants were categorized into the control (n = 49 cases) and research groups (n = 50 cases) receiving routine and multi-channel continuous nursing care, respectively. Comparative analysis involved data on postoperative rehabilitation (time to first anal exhaust, oral feeding and ambulation, and hospital stay), complications (nausea and vomiting, delayed gastric emptying, and abdominal distension), NEs [Self-rating Anxiety (SAS)/Depression Scale (SDS)], treatment compliance, self-efficacy, and QoL [World Health Organization QoL Brief Version (WHOQOL-BREF)].

RESULTS

Compared to the control group, the research group demonstrated earlier first postoperative anal exhaust, oral feeding, and ambulation, shorter hospital stay,

lower POC rate, and more reduced SAS and SDS scores postintervention, which was significantly lower than the baseline. The treatment compliance scores were significantly higher in the research group than in the control group in terms of medication adherence, daily exercise, reasonable diet, and regular review. Further, the research group demonstrated increased self-efficacy scores in terms of positive attitude, self-stress relief, and self-decision-making, as well as the overall score postintervention, which were higher than the control group. Moreover, the research group reported notably higher WHOQOL-BREF scores in domains such as physiology, psychology, social relations, and environment.

CONCLUSION

Multi-channel continuous nursing intervention prevents POCs in patients undergoing RGE for GC as well as significantly alleviates patients' NEs and boosts their QoL.

Key Words: Radical gastrectomy; Multi-channel continuous nursing; Postoperative complications; Negative emotions; Quality of life

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Core Tip: This study enrolled 99 patients who underwent radical gastrectomy (RGE) for gastric carcinoma (GC). A comprehensive analysis involved the clinical advantages of multi-channel continuous nursing intervention from multiple dimensions, including postoperative rehabilitation, complications, negative emotions, treatment compliance, self-efficacy, and quality of life. Our data support that the application of multi-channel continuous nursing intervention in patients post-RGE effectively facilitates postoperative recovery, reduces the risk of postoperative complications, alleviates negative psychological states, and significantly improves treatment compliance, self-efficacy, and the overall quality of life. The results provide effective measures and recommendations for treating patients post-RGE for GC. Moreover, it is considered a reference for providing more optimal nursing care alternatives in the postoperative nursing interventions for such patients, thereby contributing to overall quality of care and patient outcome improvements.

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INTRODUCTION

Gastric carcinoma (GC) is a gastrointestinal tumor that originates from the cardia or more distant gastric region, pathogenically caused by *Helicobacter pylori* infection, dietary habits, family history, alcohol abuse, smoking, genetic susceptibility, *etc*.[1,2]. Relevant epidemiological data indicated that the disease afflicted over 1.08 million individuals globally in 2020 and caused approximately 800000 deaths, with large geographical differences in the age-standardized incidence and mortality rates of GC worldwide[3,4]. At present, radical gastrectomy (RGE), perioperative chemotherapy, adjuvant chemotherapy, and adjuvant chemoradiotherapy are the primary treatment strategies for GC, among which RGE exerts a high advantage in reducing the risk of GC-related mortality[5]. This treatment demonstrates a certain effectiveness; however, it carries a certain risk of postoperative complications (POCs), especially among middle-aged and elderly patients with functional decline[6,7]. This may inevitably result in negative emotions (NEs) in patients, affecting their treatment outcomes and quality of life (QoL)[8]. Given this, providing a reliable nursing intervention is important for preventing POCs in patients with RGE, alleviating NEs, and boosting QoL.

The nursing service provided by routine nursing is basic but has difficulty playing a significant role in promoting postoperative rehabilitation or matching the increasing health requirements of patients[9]. Conversely, multi-channel continuous nursing intervention is a care mode that primarily provides diet, work and rest, psychology, rehabilitation, cognition, and other services for discharged patients. It provides multi-channel services for patients with the help of network platforms in addition to health education, telephone interviews, re-examination, *etc*.[10]. This model not only makes it easy to grasp patients' physical conditions and potential problems but also helps nurses respond appropriately to the patient's condition promptly to prevent symptoms from worsening[11,12]. Fan *et al*[13] revealed that multi-channel continuous nursing intervention effectively helped patients with GC to achieve symptom management and timely improved their postoperative gastrointestinal function and QoL. Besides the application in patients with GC, this care model has been applied to patients undergoing glioma surgery and those elderly with rectal cancer, demonstrating advantages in NE relief; QoL, self-efficacy, and sleep quality improvement; and POC prevention[14,15].

This report assumes that multi-channel continuous nursing intervention exerts a significant positive effect on POC and NE prevention and QoL improvement in patients with GC post-RGE, and is hereby analyzed, verified, and reported.

MATERIALS AND METHODS

Patient information

This retrospective study included 99 patients undergoing RGE for GC in our hospital from May 2020 to May 2023. The control group (Con; n = 49) received routine care, whereas the research group (Res; n = 50) received multi-channel continuous nursing interventions. The Con and Res demonstrated clinical comparability with no notable difference in baseline data.

Criteria for patient enrollment and exclusion

Eligibility criteria: All patients were diagnosed with GC, underwent laparoscopic-assisted RGE, and met the Nutritional Risk Screening (NRS2002) criteria[16], with complete medical records. Further, patients had normal communication and cognitive abilities and agreed to cooperate with the study.

Exclusion criteria: Hospital referrals or patients who gave up treatment, with surgical contraindications, complicated with serious cardio-cerebrovascular diseases or renal dysfunction, suffering from coagulation dysfunction or autoimmune system defects, and with other malignancies.

Methods

Routine continuous nursing measures were implemented in the Con. Specific contents: According to the patient's situation, the patient and his/her family received routine health education, including specific medication, diet rules, points for attention in activities and rest, and specific return visit times. Further, the patient's daily exercise and dietary regimen was made into a detailed publicity material, which was distributed to the patient upon discharge. Telephone follow-ups were conducted at least twice a month within 3 months postoperatively.

The Res received multi-channel continuous nursing intervention, specifically the following: (1) Setting up a continuous nursing service group. The head nurse and attending physician were appointed as the team leaders, whereas the team members were composed of five specialist nurses, all of whom had more than 3 years of working experience. All team members received special training to master the relevant knowledge and skills post-RGE, with good communication skills and service awareness to proactively provide help to patients; (2) Mobile platform intervention. The network platform was utilized to conduct continuous nursing care for patients. The nursing staff fully used the flexibility of the network platform and the WeChat public account as well as established a WeChat group and let patients enter the group by scanning the QR code. Attending doctors and responsible nurses answered patients' doubts online daily in the WeChat group and encouraged patients to express their condition every day as well as their experiences and feelings to meet their social needs and achieve mutual communication and mutual encouragement. Furthermore, the predominant problems were sorted out, relevant treatment measures were recommended through the public account, and the specific self-care methods were uploaded to the WeChat official account so that patients could inquire at any time. Moreover, regular diet and exercise were recommended to improve patients' cognitive levels and compliance; and (3) Life guidance. The nursing staff strengthened the relevant health knowledge post-RGE and established a targeted health explanation program based on the complicated psychological changes of patients. Besides, the importance of a reasonable diet was emphasized to the patients, namely, avoiding spicy stimulation, eating more low-fat foods, ensuring a diverse diet, guaranteeing balanced nutrition intake, reducing salt intake, and encourage encouraging drinking water. For those with a history of smoking and drinking, the importance of quitting smoking and drinking was highlighted for those with a smoking and drinking history, and the family members were encouraged to supervise and give provide patients support.

Analysis indexes

Postoperative rehabilitation: The time to first postoperative anal exhaust, oral feeding, and ambulation, and the hospital stay of both groups were observed and documented.

POCs: Cases of adverse events, such as nausea and vomiting, delayed gastric emptying, and abdominal distension, were observed and recorded, and the incidence rate was calculated.

Nes: We utilized the Self-rating Anxiety Scale (SAS)/Self-rating Depression Scale (SDS)[17] to assess patients' anxiety and depression pre- and postintervention. Both scales have 20 items and a total score of 80 points, with higher scores indicating more serious NEs.

Treatment compliance: Based on the self-made treatment compliance questionnaire for postoperative patients with GC developed by our hospital, patients were assessed for treatment compliance in terms of medication adherence, daily exercise, reasonable diet, and regular review. Each dimension has a maximum score of 20 points, and the score is directly proportional to treatment compliance.

Self-efficacy: The patients' self-efficacy pre- and postintervention was assessed based on the General Self-Efficacy Scale [18], including positive attitude, self-stress relief, and self-decision-making. The total score ranges from 28 to 140 points, with the score positively related to self-efficacy.

QoL: Patients' QoL was evaluated with the World Health Organization QoL Brief Version (WHOQOL-BREF)[19], which primarily included 26 items in the fields of physiology, psychology, social relations, and environment. Each item was recorded with 1-5 points, and a higher score indicated a better QoL in each field.

Table 1 Baseline data of two groups of patients following radical gastrectomy, *n* (%)

Classification	Control group (*n* = 49)	Research group (*n* = 50)	χ^2/t	*P* value
Age (years)	62.53 ± 5.56	64.32 ± 7.31	1.369	0.174
Gender			0.845	0.358
Male	30 (61.22)	35 (70.00)		
Female	19 (38.78)	15 (30.00)		
Body mass index (kg/m^2)	22.18 ± 2.24	22.94 ± 2.56	1.571	0.120
NRS2002 (points)	3.08 ± 0.76	3.14 ± 1.11	0.313	0.755
Diabetes			0.260	0.610
With	15 (30.61)	13 (26.00)		
Without	34 (69.39)	37 (74.00)		
Hypertension			0.246	0.620
With	18 (36.73)	16 (32.00)		
Without	31 (63.27)	34 (68.00)		
Hyperlipidemia			0.845	0.358
With	19 (38.78)	15 (30.00)		
Without	30 (61.22)	35 (70.00)		

NRS2002: Nutritional Risk Screening.

Table 2 Impact of multi-channel continuous nursing on postoperative complications in patients following radical gastrectomy, *n* (%)

Classification	Control group (*n* = 49)	Research group (*n* = 50)	χ^2	*P* value
Nausea and vomiting	8 (16.33)	1 (2.00)		
Delayed gastric emptying	1 (2.04)	0 (0.00)		
Abdominal distension	0 (0.00)	1 (2.00)		
Total	9 (18.37)	2 (4.00)	5.172	0.023

Statistical analysis

In this study, both continuous (mean ± SE) and categorical [number of cases/percentage (*n*/%)] variables were imported into Statistical Package for the Social Sciences version 19.0 for statistical analyses. Among them, the χ^2 test was utilized to compare categorical variables, and the independent sample *t*-test was used to compare continuous variables between groups. *P* values of < 0.05 indicated statistical significance.

RESULTS

Baseline data of the two groups of patients with GC post-RGE

Baseline data analysis revealed no obvious inter-group differences in terms of age, gender, body mass index, NRS2002, diabetes, hypertension, and hyperlipidemia ($P > 0.05$; Table 1).

Effect of multi-channel continuous nursing intervention on postoperative rehabilitation in patients post-RGE

The postoperative rehabilitation assessment revealed that the Res had a markedly shorter time to first anal exhaust, oral feeding, and ambulation, as well as reduced hospital stay than the Con ($P < 0.05$; Figure 1).

Influence of multi-channel continuous nursing intervention on POCs in patients post-RGE

The Con demonstrated a higher incidence of nausea and vomiting, delayed gastric emptying, and abdominal distension than the Res ($P < 0.05$; Table 2).

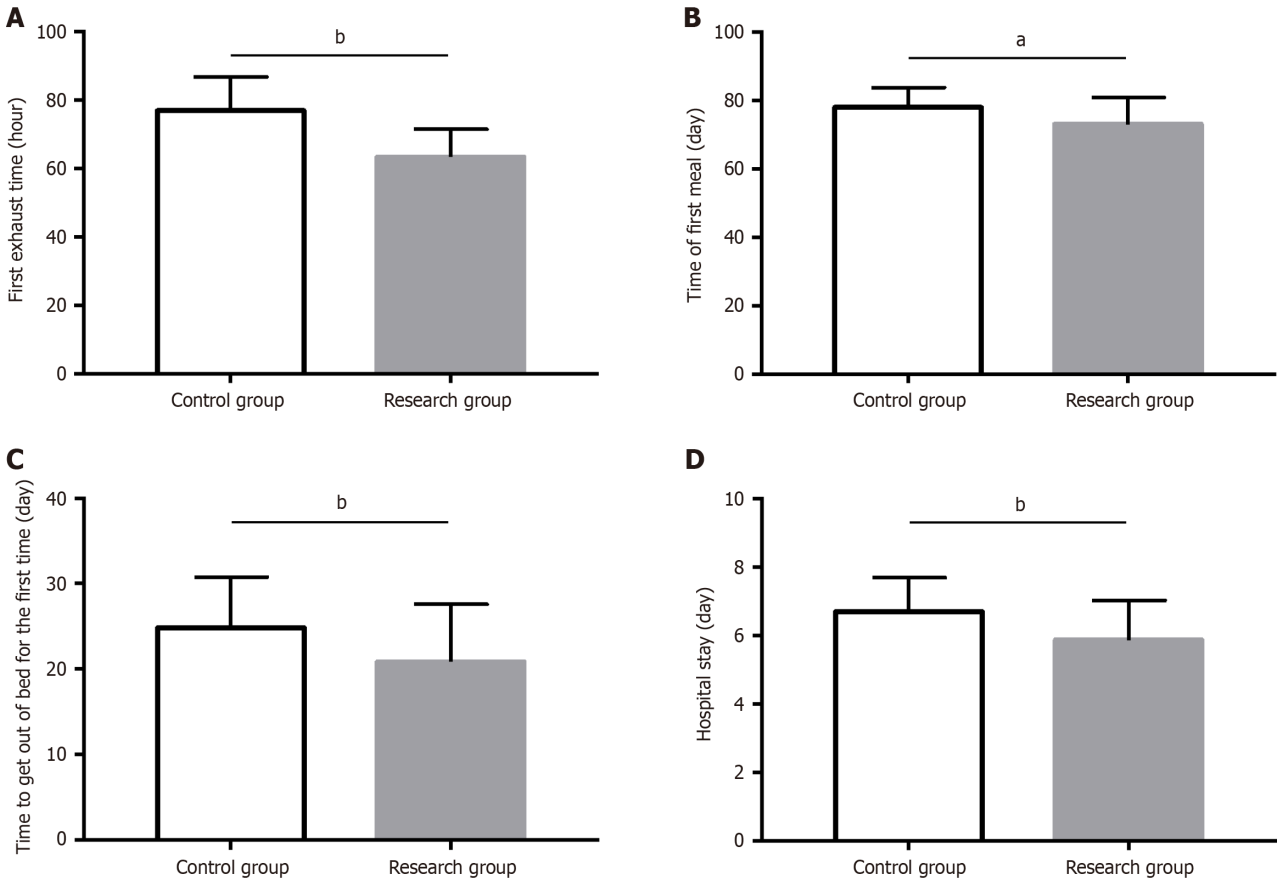


Figure 1 Influence of multi-channel continuous nursing on postoperative rehabilitation of patients after radical gastrectomy. A: Influence of multi-channel continuous nursing on the first exhaust time of patients after radical gastrectomy (RGE); B: Influence of multi-channel continuous nursing on the first oral feeding of patients after RGE; C: Influence of multi-channel continuous nursing on the first ambulation after RGE; D: Influence of multi-channel continuous nursing on hospital stay of patients after RGE. $^{a}P < 0.05$ and $^{b}P < 0.01$, respectively.

Impact of multi-channel continuous nursing intervention on NEs in patients post-RGE

Anxiety and depression assessment revealed no marked inter-group difference in SAS and SDS preintervention ($P > 0.05$); however, the two scores were significantly reduced after nursing care, with even lower scores in the Res ($P < 0.05$; Figure 2).

Effect of multi-channel continuous nursing intervention on treatment compliance in patients post-RGE

The Res demonstrated significantly higher treatment compliance in domains such as medication adherence, daily exercise, reasonable diet, and regular review, compared to the Con ($P < 0.05$; Figure 3).

Impact of multi-channel continuous nursing intervention on self-efficacy in patients post-RGE

The General Self-Efficacy Scale was utilized to assess the self-efficacy of patients pre- and postintervention. The two groups did not differ much in preinterventional self-efficacy scores in positive attitude, self-stress relief, and self-decision-making domains as well as the total score ($P > 0.05$). Postintervention, the scores of both groups in all the above aspects significantly increased ($P < 0.05$), especially in the Res ($P < 0.05$; Figure 4).

Effect of multi-channel continuous nursing intervention on QoL in patients post-RGE

The WHOQOL-BREF scale was utilized to assess patients' QoL. The data revealed that the study group demonstrated significantly higher QoL scores in physiological, psychological, social relations, and environmental fields than the Con ($P < 0.05$; Figure 5).

DISCUSSION

So far, no study has confirmed the positive effects of multi-channel continuous care on POCs, NEs, and QoL of patients post-RGE. This report conducted a relevant analysis to fill this gap and confirm the effectiveness of its application in such patients.

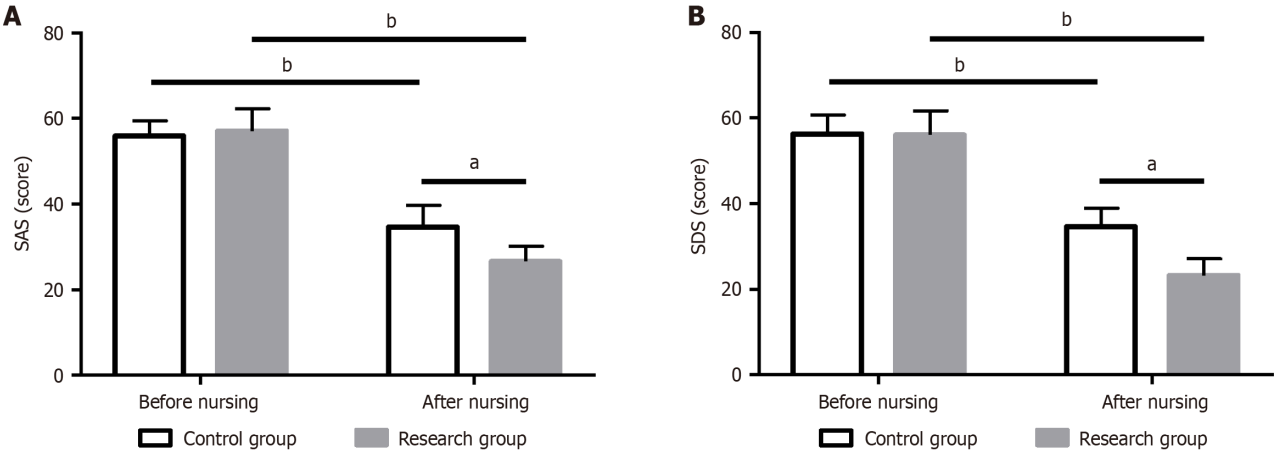


Figure 2 Influence of multi-channel continuous nursing on negative emotions of patients after radical gastrectomy. A: Impact of multi-channel continuous nursing on Self-rating Anxiety Scale scores of patients after radical gastrectomy (RGE); B: Impact of multi-channel continuous nursing on Self-rating Depression Scale scores of patients after RGE. [a]*P* < 0.05 compared with the control group; [b]*P* < 0.01 compared with the score before nursing; SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale.

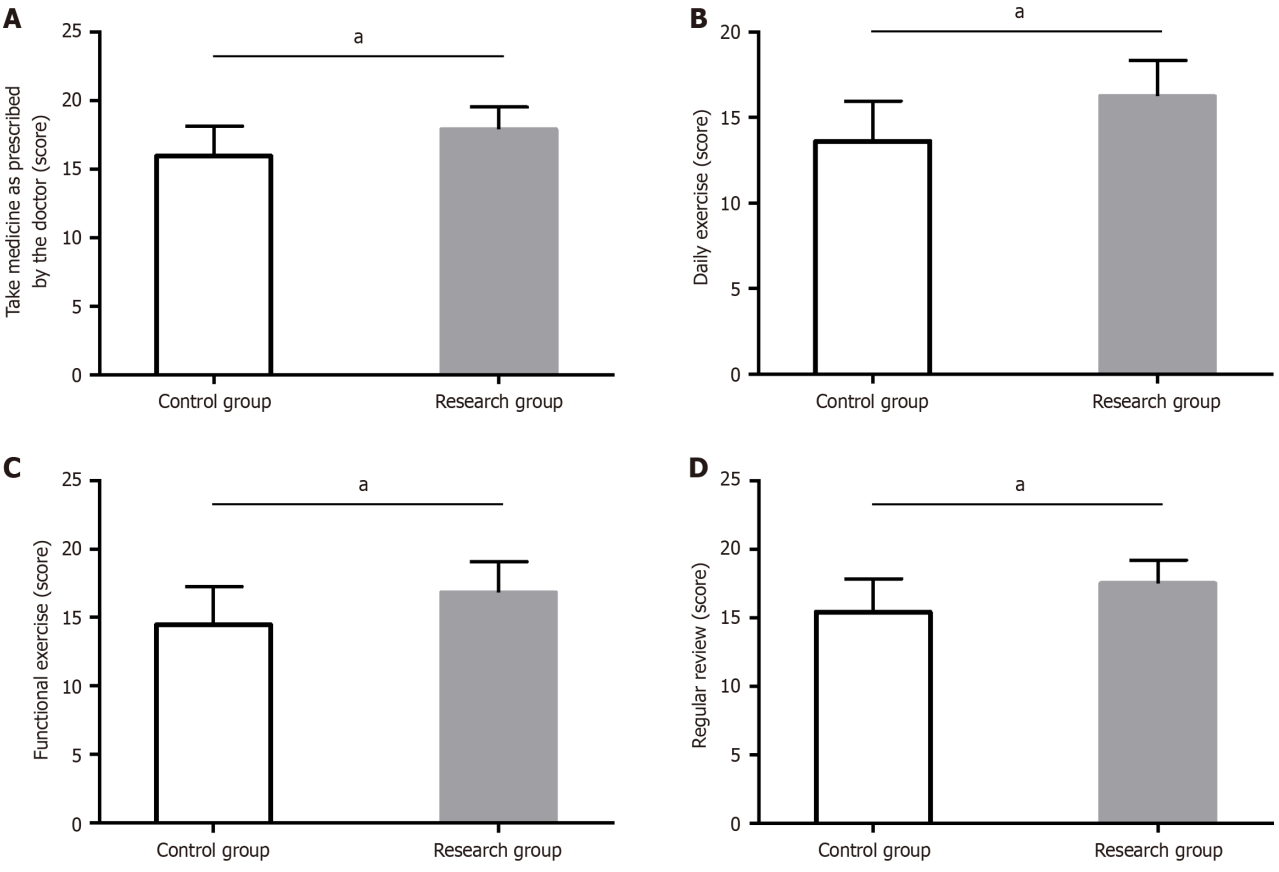


Figure 3 The impact of multi-channel continuous nursing on treatment compliance of patients after radical gastrectomy. A: The impact of multi-channel continuous nursing on the treatment compliance of patients after radical gastrectomy (RGE) in terms of medication adherence; B: The impact of multi-channel continuous nursing on the treatment compliance of post-RGE patients in terms of daily exercise; C: The impact of multi-channel continuous nursing on treatment compliance in terms of reasonable diet in post-RGE patients; D: The impact of multi-channel continuous nursing on treatment compliance in terms of regular review in post-RGE patients. [a]*P* < 0.05.

In recent years, RGE has been continuously enhanced to preserve gastric function as much as possible[20]. However, the risk of complications in patients post-RGE remains as high as 25%, which not only impairs their QoL but also negatively affects their survival outcomes[21]. In this study, we first assessed postoperative rehabilitation and revealed that the Res had significant advantages in postoperative rehabilitation, mainly manifested as markedly shortened first postoperative anal exhaust, oral feeding, ambulation, and hospital stay than the Con, indicating the significant role of multi-channel continuous nursing intervention in promoting postoperative rehabilitation in patients with GC post-RGE.

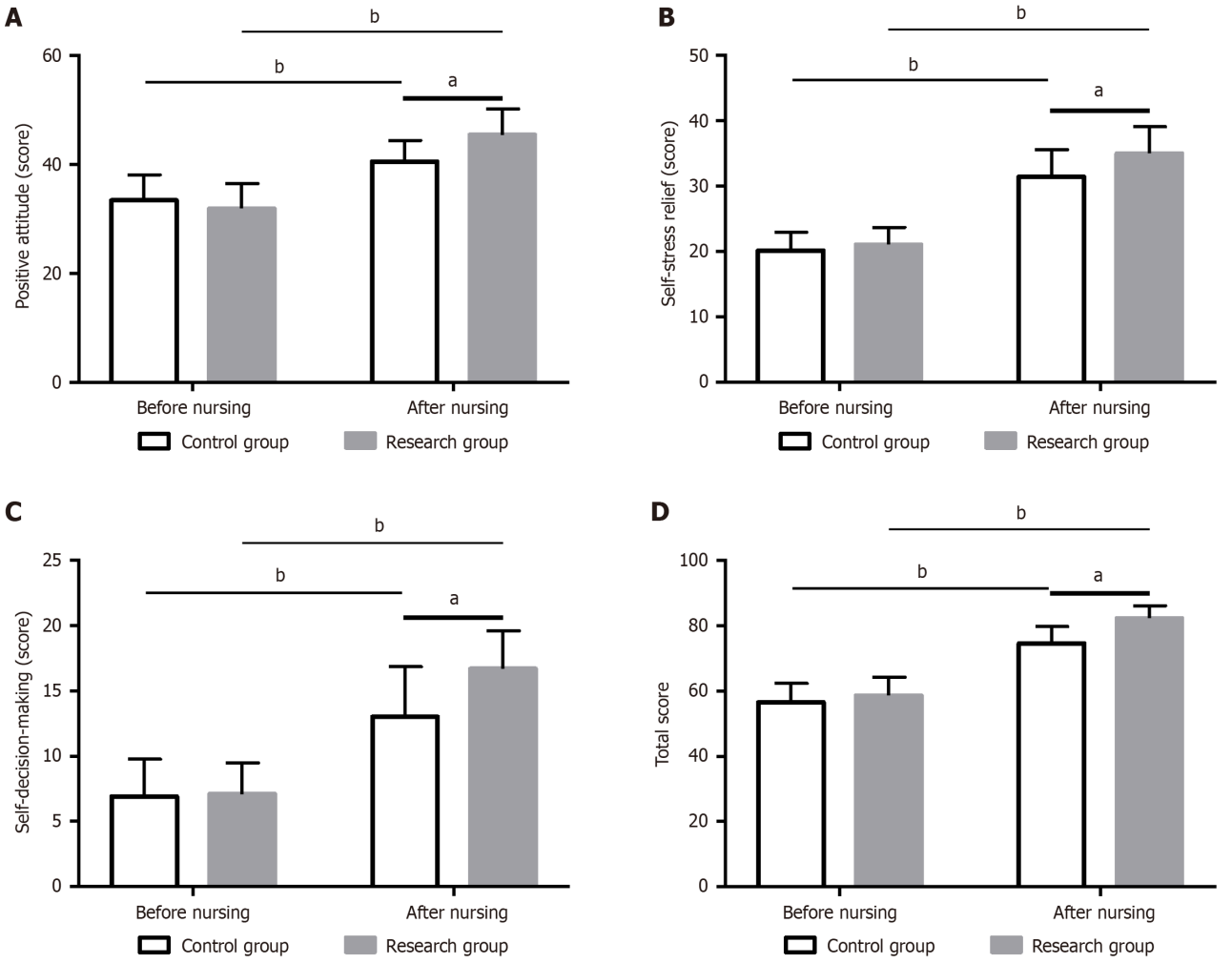


Figure 4 The impact of multi-channel continuous nursing on self-efficacy of patients after radical gastrectomy. A: The impact of multi-channel continuous nursing on positive attitudes of patients after radical gastrectomy (RGE); B: The impact of multi-channel continuous nursing on self-stress relief in patients after RGE; C: The impact of multi-channel continuous nursing on self-decision-making of patients after RGE; D: The impact of multi-channel continuous nursing on the total score of patients after RGE. $^{a}P < 0.05$ compared with the control group; $^{b}P < 0.01$ compared with the score before nursing.

Furthermore, the total complication rates of nausea and vomiting, delayed gastric emptying, and abdominal distension were statistically lower in the Res than in the Con, indicating the significant preventive effect of multi-channel continuous nursing intervention against POCs in patients post-RGE. Hu *et al*[22] demonstrated that the use of multi-channel continuous care in patients undergoing GC surgery not only significantly shortened the time to anal exhaust, defecation, food intake, and bowel sound recovery to promote gastrointestinal recovery but also effectively reduced the risk of POCs, which is consistent with our research findings. Due to the convenience of the online platform, the multi-channel continuous nursing intervention strengthens disease understanding and POC prevention by answering questions online for patients daily, which helps patients achieve effective recovery and prevents some adverse event occurrences to a certain extent. The results of NEs revealed that the SAS and SDS in the Res postintervention were significantly lower than the baseline and the Con, indicating that NEs are significantly alleviated after multi-channel continuous nursing interventions. This may be associated with the humanistic care provided to patients post-RGE in the process of multi-channel continuous nursing intervention, which takes care of patient's emotions and provides timely psychological counseling while helping them establish a correct disease understanding, thereby aiding in dispelling part of patients' anxiety and establishing a positive mentality for them to overcome the disease[23,24]. Rui *et al*[25] revealed that the application of multi-channel continuous nursing intervention to patients with GC effectively reduced the generation of NEs and significantly improved their self-care ability, similar to our research results. We assessed treatment compliance from aspects such as medication adherence, daily exercise, reasonable diet, and regular review. The Res had significant clinical advantages compared to the Con in all the above-mentioned aspects, indicating that multi-channel continuous nursing intervention significantly improves the treatment compliance of patients post-RGE. Fu *et al*[26] indicated that the application of targeted nursing intervention combined with psychological intervention in patients with GC undergoing chemotherapy improves patients' mental well-being, promotes healthy behaviors, and enhances treatment compliance, which is similar to our observations. Subsequently, the assessment data on the General Self-Efficacy Scale revealed significantly higher scores of the Res than the Con in terms of positive attitude, self-stress relief, self-decision-making, and the total score postintervention, indicating that the use of multi-channel continuous nursing intervention for patients post-RGE significantly improved their self-efficacy. Yin *et al*[27] demonstrated that the deployment of a nursing

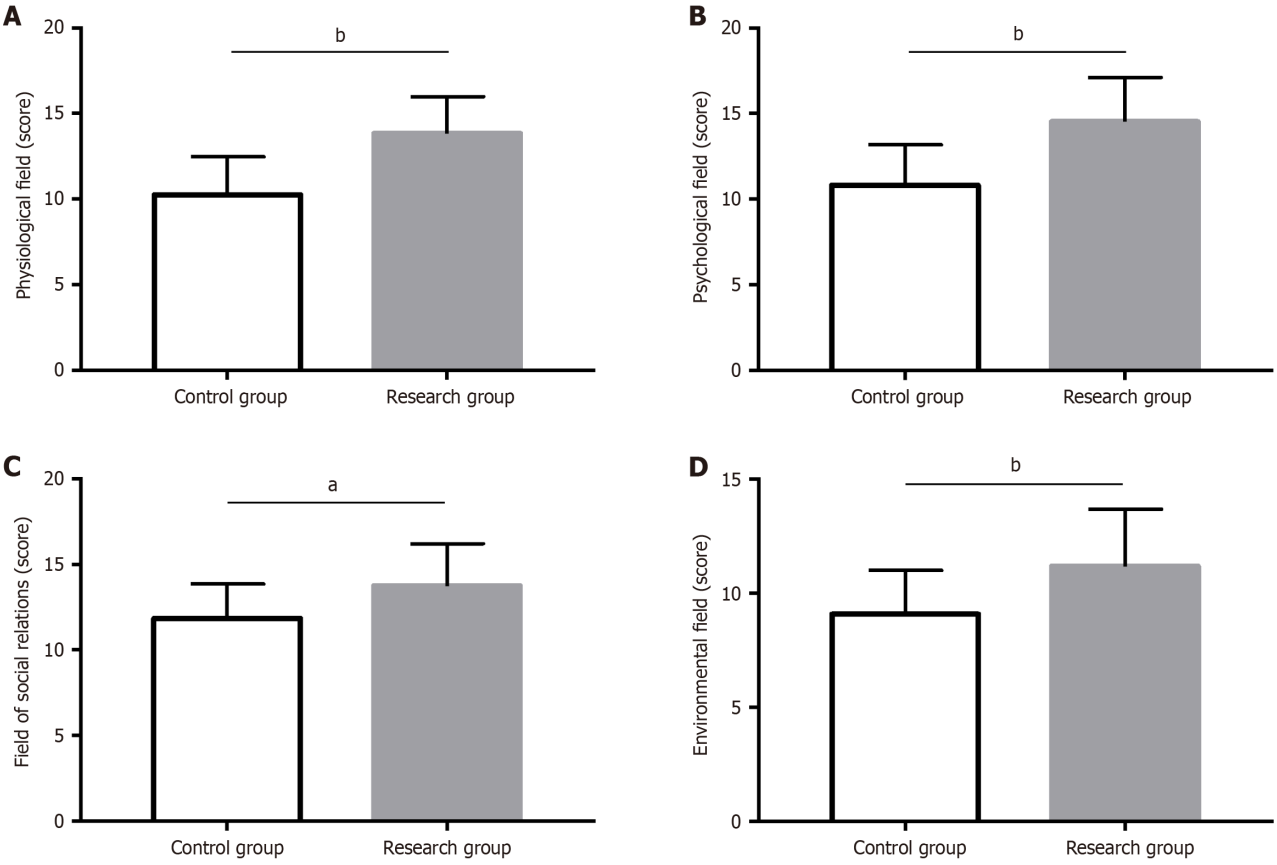


Figure 5 Influence of multi-channel continuous nursing on quality of life of patients after radical gastrectomy. A: Influence of multi-channel continuous nursing on physiological field scores of patients after radical gastrectomy (RGE); B: Influence of multi-channel continuous nursing on psychological field scores of patients after RGE; C: Influence of multi-channel continuous nursing on social relations scores of patients after RGE; D: Influence of multi-channel continuous nursing on environmental field scores of patients after RGE. $^{a}P < 0.05$ and $^{b}P < 0.01$, respectively.

intervention based on the Information-Knowledge-Attitude-Practice model among patients with GC catalyzes the construction of a comprehensive and accurate understanding of the disease and self-management concepts. This, in turn, significantly contributes to the augmentation of patients' self-management capabilities, which supports the results of our investigation. After QoL assessment, the Res was advantageous over the Con in WHOQOL-BREF scores from the fields of physiology, psychology, social relations, and environment, indicating that multi-channel continuous nursing intervention significantly improves the QoL of patients post-RGE, similar to the research results of Zhang *et al*[28]. Liu *et al*[29] revealed that multi-channel continuous nursing intervention not only promoted the long-term functional recovery of elderly patients with hip fractures, relieved NEs, and reduced the risk of POCs, but also exerted a significant positive effect on improving patients' QoL, which is congruent with our observations. Furthermore, many researchers have dedicated their efforts to the meticulous refinement of the multi-channel continuous nursing intervention experience. For instance, Calton *et al*[30] postulated that the integration of multi-channel continuous nursing intervention with telemedicine can confer survival advantages upon patients with cancer, including those with GC. This is particularly beneficial for individuals grappling with functional impairments, a high symptom burden, or those facing economic and geographical constraints. Zhang *et al*[31] introduced the proposition that the combination of multi-channel continuous nursing intervention with smart nursing wheelchairs not only results in a remarkable improvement in the operational efficiency of nursing personnel but also increases the overall quality and experience of nursing care, better meeting the daily needs of elderly patients or those with disabilities.

The possibility and potential advantages of integrating multi-channel extended care with other emerging nursing concepts or technologies are extremely significant and should not be underestimated in the slightest. This integration model not only opens up a new perspective for subsequent studies and expands more diverse research directions but also introduces new vitality to the innovative development of the nursing field. We plan to conduct in-depth research in this regard in the future, actively investigate the best practices of this integration, strive to achieve more significant breakthroughs in the nursing experience, and thus provide patients with higher-quality, more efficient, and personalized nursing services.

CONCLUSION

Conclusively, multi-channel continuous nursing intervention helps not only facilitate the postoperative rehabilitation of

patients post-RGE, but also prevent POCs, relieve anxiety and depression, and improve treatment compliance, self-efficacy, and QoL, which provide effective measures and suggestions for treating patients with GC post-RGE.

FOOTNOTES

Author contributions: Luo HL designed the research and wrote the first manuscript; Luo HL and Luo HL 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.

Institutional review board statement: This study was approved by the Ethic Committee of Henan Vocational College of Nursing.

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

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

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy of modified pancreatic duct stent drainage during endoscopic retrograde cholangiopancreatography for common bile duct stones

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Abstract

BACKGROUND

Common bile duct stones pose a high risk of recurrence or disease progression if not promptly treated. However, there is still no optimal treatment approach.

AIM

To investigate the clinical efficacy of modified pancreatic duct stent drainage in endoscopic retrograde cholangiopancreatography (ERCP) for treating common bile duct stones.

METHODS

This retrospective study included 175 patients with common bile duct stones treated at Taizhou Fourth People's Hospital between January 1, 2021, and November 30, 2023. The patients were divided into three groups-the modified pancreatic duct stent drainage group (59 cases), the nasobiliary drainage group (58 cases), and the standard biliary drainage group (58 cases). Preoperative general clinical data, laboratory indicators, and the visual analog scale (VAS) at two time points (24 hours before and after surgery) were compared, along with postoperative complications across the three groups.

RESULTS

Serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, total bilirubin, direct bilirubin, C-reactive protein, and amylase were significantly lower in the modified pancreatic duct stent drainage group and the standard biliary drainage group than those in the nasobiliary drainage group ($P < 0.05$). However, no statistically significant differences were observed in white blood cells, hemoglobin, or neutrophil levels

among the three groups ($P > 0.05$). The standard biliary drainage group had significantly lower VAS scores [(4.36 ± 1.18) points] than those for the modified pancreatic duct stent drainage group [(4.92 ± 1.68) points] ($P = 0.033$), and the nasobiliary drainage group [(5.54 ± 1.24) points] ($P = 0.017$). There were no statistically significant differences in complication rates across the three groups ($P > 0.05$).

CONCLUSION

Compared to standard biliary drainage and nasobiliary drainage, the modified pancreatic duct stent used during ERCP for patients with bile duct stones significantly reduced hepatocyte injury, improved liver function parameters, alleviated inflammation and pain, enhanced patient comfort, and demonstrated superior safety.

Key Words: Modified pancreatic duct stent drainage; Endoscopic retrograde cholangiopancreatography; Common bile duct stones; Curative effect; Complications

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Core Tip: There is currently a paucity of multidimensional comparative analyses concerning the clinical efficacy of modified pancreatic duct plastic stents for endoscopic retrograde biliary drainage, endoscopic nasobiliary drainage, and Christmas tree-shaped plastic stents for standard biliary drainage following endoscopic retrograde cholangiopancreatography (ERCP) for common bile duct stone removal. This study addresses this gap with a comprehensive analysis. Our findings reveal that compared to standard biliary drainage and nasobiliary drainage, modified pancreatic stents offer significant benefits, including a significant reduction in hepatocyte damage, improvement in liver function parameters, alleviated inflammation and pain, enhanced patient comfort, and increased treatment safety. Therefore, we recommend modified pancreatic plastic stents as the preferred post-ERCP drainage method for patients with common bile duct stones.

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INTRODUCTION

Cholelithiasis of the common bile duct refers to the presence of stones at the distal end of the common bile duct. These stones are typically a mixture, with bile pigment stones being the most common type. The causes of choledocholithiasis in patients with choledochal cholelithiasis are multifaceted, resulting from factors such as cholangitis, roundworm infestations, and bile stasis. The etiology of the disease is complex, leading to a wide range of clinical manifestations, such as epigastric cramps, chills, and penetrating low back pain[1]. Choledochal stones occur in approximately 5%-20% of patients with cholelithiasis and in about 10% of those who undergo cholecystectomy[2,3]. Relevant epidemiological data showed that cholelithiasis is the most common biliary tract disease in the United States, with a mortality rate of 260.8 deaths per 100000 people. Each year, approximately 180000 patients receive treatment for cholelithiasis, while over 700000 undergo surgical procedures related to the condition[4]. Studies indicate that the incidence of common bile duct stones ranges from approximately 5% to 20%, with an increasing trend over time[5]. More than 20% of affected patients present with clinical symptoms such as fever, abdominal pain, and jaundice. In severe cases, complications, such as acute obstructive suppurative cholangitis and septic shock, may occur[6]. If left untreated, gallstones can lead to recurrent symptoms and disease progression, highlighting the critical need for timely and effective stone removal[7].

Currently, endoscopic retrograde cholangiopancreatography (ERCP) serves as a cornerstone in the clinical treatment of bile duct stones, effectively alleviating symptoms and facilitating their complete removal[8]. Image-guided techniques are essential in enhancing the precision and success of surgical interventions. Since its development in the 1960s, ERCP has evolved into a widely used procedure for managing common bile duct stones. It is an imaging technique involving the insertion of a catheter through a duodenoscope into the pancreaticobiliary duct opening at the ampulla of Vater. By injecting contrast dye through the scope, ERCP allows visualization of the pancreato-biliary system, enabling precise identification of stone count, location, assessment of biliary pressure, and evaluation of the papilla's function. ERCP offers advantages such as minimal invasiveness and rapid recovery[9]. However, it is a technically demanding procedure with a relatively high risk of complications, ranging from 5% to 10%[10]. Common complications following ERCP include wound infection, pancreatitis, cholangitis, hemorrhage, perforation, and hyperamylasemia, which can significantly affect patients' postoperative recovery and overall well-being, limiting its clinical use[10-12]. To improve surgical outcomes, clinicians often use biliary stenting to reduce biliary pressure, support wound healing, and facilitate inflammation resolution while aiding in the removal of residual stones from the bile duct.

Stent drainage procedures include both standard biliary drainage and endoscopic retrograde biliary drainage (ERBD)[13]. The Christmas tree-shaped plastic stent is commonly used in clinical practice for biliary drainage due to its low risk of spontaneous detachment. Guidelines[14] recommend removal after 3 to 6 months; however, repeated removals may

increase treatment costs, psychological burden, and the risk of complications. Research has shown that endoscopic nasobiliary drainage (ENBD) is a minimally invasive and relatively straightforward endoscopic technique that can achieve bile duct drainage outcomes comparable to traditional surgery, with minimal trauma and endoscopic intervention, while potentially reducing the risk of complications following ERCP[15]. Park *et al*[16] reported that using pancreatic plastic stents for biliary internal drainage resulted in significant drainage outcomes. Similarly, a study by He *et al*[17] demonstrated that modified pancreatic stents effectively prevented post-ERCP pancreatitis, with a self-removal rate of 84.21% after 14 days.

Currently, there is no standardized consensus on the optimal surgical approach for biliary drainage in clinical practice, highlighting the need for further research to establish a unified strategy. Additionally, no multidimensional comparative analysis has been conducted to evaluate the clinical efficacy of using a modified pancreatic duct plastic stent for ERBD or ENBD and a Christmas tree-shaped plastic stent for standard biliary drainage following ERCP for bile duct stone removal. Therefore, in this study, we compared the clinical efficacy of the modified pancreatic duct plastic stent for ERBD, ENBD, and Christmas tree-shaped plastic stents in ERCP for treating common bile duct stones. We aim to explore the effectiveness of the improved pancreatic duct plastic stent in patients with ERCP and its impact on postoperative complications, thereby identifying the most suitable drainage technique after ERCP for common bile duct stones and improving patient outcomes.

MATERIALS AND METHODS

Patients

This retrospective study included 175 patients with choledocholithiasis admitted to Taizhou Fourth People's Hospital between January 1, 2021, and November 30, 2023. The patients were divided into three groups-the modified pancreatic duct stent drainage group (using ERBD technology, n = 59), the nasobiliary drainage group (using ENBD technology, n = 58), and the standard biliary drainage group (using Christmas tree-shaped stent, n = 58). The patient inclusion process is graphically illustrated in Figure 1.

The inclusion criteria were as follows: Diagnosis of choledocholithiasis according to the 2019 European Society of Gastrointestinal Endoscopy clinical practice guidelines[18]; confirmation of gallstones in the biliary ducts through histopathological examination or imaging techniques, such as laparoscopy[19]; pre-treatment abdominal pain of varying degrees, with a visual analog scale (VAS) score of 5 or higher; adherence to treatment protocols; and all surgeries performed by the same surgical team. Patients were excluded if they had any of the following: Significant organ dysfunction (heart, liver, or kidney), not meeting the indications for ERCP, severe digestive system impairment, concurrent malignant tumors, or poor compliance or refusal to participate.

Approaches to intervention

Surgical equipment: The following surgical equipment was utilized during the interventions: An electronic duodenoscope (TJF260V by Olympus Corporation, Japan), guidewire (Yellow Stripe, 0.035 inches or 4500 mm, Nanjing Minimally Invasive Medical Technology Co., Ltd.), papillotome (Medi-Globe GmbH), forceps, balloon catheter (Nanjing Minimally Invasive Medical Technology Co., Ltd.), stone retrieval basket (Cook Medical), Christmas tree-shaped plastic stent (8.5 Fr, Nanjing Minimally Invasive Medical Technology Co., Ltd.), standard nasobiliary drainage tube (NBDS-B-7/250-P, Nanjing Minimally Invasive Medical Technology Co., Ltd.), and a modified pancreatic duct stent (SPSOF-7-5, Cook Medical).

ERCP procedure: All patients underwent routine blood tests, liver and kidney function assessments, coagulation function evaluations, and imaging examinations 24 hours before the operation. They were required to fast and refrain from food and water for at least 6 hours before the operation. After positioning the patients prone, they received routine anesthesia and analgesia. The endoscope was then inserted through the mouth to reach the duodenal papilla. Selective choledochal intubation was performed using a papillotome knife with a guidewire, followed by an injection of a 20% iophedronol contrast. The choledochal ducts were observed using C-arm fluoroscopy. During the procedure, endoscopic sphincterotomy and endoscopic balloon dilatation were performed based on the location and size of the stones, as well as the diameter of the bile duct. After stone extraction using a balloon or mesh basket, re-imaging was performed to confirm the complete clearance of the stones.

Drainage procedure: In the modified pancreatic duct stent drainage group, following cholecystectomy for gallstones and ERBD, a modified pancreatic duct plastic stent (COOK Company) was inserted into the pancreatic duct. Correct placement of the stent was confirmed using intraoperative C-arm fluoroscopy. The papilla and the field of vision were free from active hemorrhage, and the endoscope was removed, marking the completion of the procedure.

In the nasobiliary drainage group, following choledochal stone extraction, an NBDS-B-7/250-P (Nanmicro Medical Technology Co., Ltd.) was inserted into the choledochus under the guidance of a guidewire. ENBD was performed. The tip of the nasobiliary tube was positioned at the openings of the left and right hepatic ducts, allowing bile outflow. C-arm fluoroscopy was used to confirm that the nasobiliary drainage tube was securely placed. The papilla and field of view were examined, revealing no active hemorrhage. The procedure was concluded by retracting the endoscope.

In the standard biliary drainage group, following choledochal stone extraction, a BPDS-13442-0807/22 Christmas tree-shaped stent (Nanjing Microtronics) was inserted into the choledochal duct for biliary drainage. C-arm fluoroscopy was used to confirm that the stent was securely placed. An examination of the papilla and the visual field showed no active

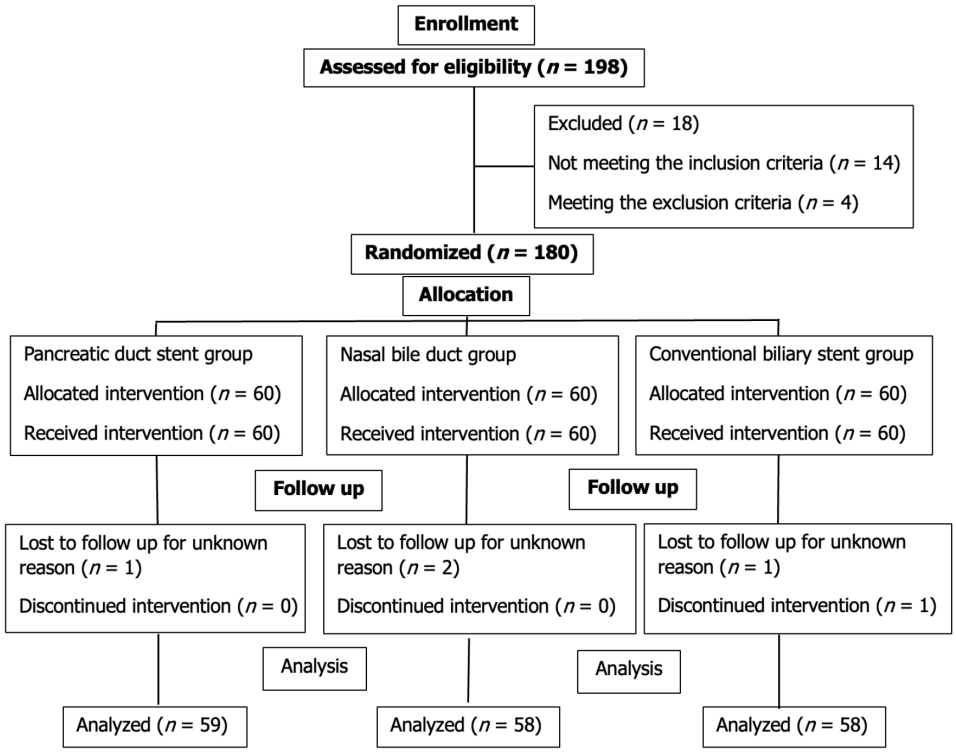


Figure 1 Flow chart of management.

hemorrhage. The procedure was concluded with the removal of the endoscope. Postoperatively, the patient's vital signs and condition should be closely monitored. Additionally, liver function, blood routine, amylase, C-reactive protein (CRP), and other relevant indices should be retested as needed. Supportive treatments, such as anti-infection measures, acid suppression, enzyme suppression, and fluid rehydration, should also be administered.

Indicator collection

General information: This study recorded and compared various parameters among the three patient groups, including age, gender, body mass index (BMI), history of alcohol consumption, time of disease onset before surgery, total hospital stay duration, disease duration, American Society of Anesthesiologists (ASA) classification, surgical duration, bile duct diameter, stone diameter, and the number of gallstones in the bile duct.

ASA classification standards[20] are as follows: Class I refers to a physically healthy individual with normal organ function; Class II describes a patient with mild systemic diseases and a surgical condition but with preserved compensatory mechanisms; Class III indicates a patient with severe systemic diseases that limits physical activity but does not preclude daily functioning; Class IV applies to a patient with severe systemic disease that is life-threatening; Class V refers to a critically ill patient who is unlikely to survive without surgical intervention; and Class VI designates a deceased patient whose organs are being prepared for transplantation.

Laboratory indicators and questionnaire surveys

Laboratory indicators, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), CRP, white blood cells (WBC), hemoglobin (Hb), neutrophils (NEU), and amylase (AMY), were measured and compared across the three patient groups before and 24 hours after drainage surgery. Pain levels were evaluated using a VAS, and postoperative complications, such as pancreatitis, cholangitis, hemorrhage, perforation, wound infection, hyperamylasemia, and mortality, were recorded.

The VAS scoring scale[21]: The scale ranges from 1 to 10, where a score of 3 or below indicates mild or no pain, a score of 4 to 6 reflects significant pain that may impact sleep, and a score of 7 or above represents severe pain with a significant impact on sleep and appetite.

Pancreatitis: This is defined by at least two of the following revised Atlanta criteria[22]: (1) Persistent upper abdominal pain attributable to pancreatitis; (2) A threefold or more significant increase in amylase or lipase levels within 24 hours postsurgery; or (3) Characteristic imaging findings on computed tomography (CT) scans, such as pancreatic enlargement, necrosis, or peripancreatic fluid collection.

Severe pancreatitis: This is characterized by peripancreatic fluid collections and/or pleural and peritoneal effusions on abdominal CT scans[23], requiring management with percutaneous catheter drainage or surgical intervention.

Cholangitis: Fever (temperature > 38 °C) occurring within 24 hours postsurgery, accompanied by elevated WBC count and abdominal pain, with no evidence of infection at another site[24].

Hemorrhage: Symptoms include black stool or hematemesis within 24 hours postsurgery, fresh blood in the nasobiliary drainage tube, and a drop in blood pressure, necessitating endoscopic hemostasis.

Perforation: Following surgery, the patient experienced worsening abdominal pain within 24 hours. Upon imaging confirmation of a perforation, the patient was managed with a medically supervised fasting regimen, gastrointestinal decompression, and antibiotic therapy for infection control. In cases of extensive perforation, prompt surgical intervention was deemed necessary.

Wound infection: Obvious redness and oozing at the surgical incision site within 24 hours postsurgery, necessitating aggressive antibiotic treatment, along with concurrent physiotherapy and other supportive care.

Hyperamylasemia: A postsurgery increase in blood amylase levels exceeding three times the upper normal limit, occurring within 24 hours without fever or abdominal pain symptoms.

Statistical analysis

Statistical analysis was conducted using IBM Statistics Version 27.0.1 (SPSS Inc., Beijing, China). In the patients' general information, gender, history of alcohol consumption, ASA classification, number of gallstones in the bile duct, and complication rates were all categorical data presented as n (%). Since the gender, ASA classification, and complication rates had theoretical frequencies > 5 and a total sample size of at least 40, Pearson's χ^2 test was applied. For the number of gallstones in the bile duct, data satisfying 1 ≥ theoretical frequency ≥ 5 and a total sample size of at least 40 were analyzed using the continuity-corrected χ^2 test (Yates' correction). Continuous data were initially analyzed for normal distribution using histograms and the Shapiro-Wilk test for single samples. In the patients' general information, variables such as age, BMI, time of disease onset before surgery, total hospital stay duration, disease duration, surgical duration, bile duct diameter, stone diameter, and all laboratory indicators, as well as VAS scores, were normally distributed and represented as (mean ± SD). The AST, ALT, ALP, GGT, TBIL, DBIL, CRP, WBC, Hb, NEU, and AMY indicators met the assumption of homoscedasticity. These variables were compared using a one-way analysis of variance (ANOVA) across the three groups. Pairwise comparisons were performed using the least significant difference t-test for all comparisons, and a one-way ANOVA with repeated measures was used to compare data collected 24 hours before and after surgery within each group. Differences were considered statistically significant when $P < 0.05$.

RESULTS

Comparison of the general clinical data of the three patient groups

Between January 1, 2021, and November 30, 2023, 175 patients with common bile duct stones successfully underwent ERCP treatment. Among them, 59 patients (33.71%) used pancreatic stent drainage, 58 patients (33.14%) employed nasobiliary drainage, and 58 patients (33.14%) utilized biliary stent drainage.

The baseline characteristics of all patients, including age, gender, BMI, history of alcohol consumption, time of disease onset before surgery, total hospital stay duration, disease duration, ASA classification, surgical duration, bile duct diameter, stone diameter, and the number of gallstones in the bile duct, are presented in Table 1. There were no statistically significant differences among the three patient groups ($P > 0.05$) (Table 1).

Comparison of laboratory indicators between the three patient groups 24 hours before and after surgery

There were no statistically significant differences in serum levels of AST, ALT, ALP, GGT, TBIL, DBIL, CRP, WBC, Hb, NEU, and AMY among the three patient groups 24 hours before surgery (all $P > 0.05$).

However, serum levels of AST, ALT, ALP, GGT, TBIL, DBIL, CRP, WBC, Hb, NEU, and AMY in all three patient groups significantly decreased 24 hours after surgery compared to 24 hours before surgery (all $P < 0.05$) (Table 2).

After adjusting for preoperative variables, different drainage methods significantly affected the changes in serum levels of AST, ALT, ALP, GGT, TBIL, DBIL, CRP, and AMY. Post-treatment comparisons showed that the modified pancreatic duct stent drainage group had significantly lower AST, ALT, ALP, GGT, TBIL, DBIL, CRP, and AMY serum levels than the nasobiliary drainage group ($P < 0.05$). Similarly, the serum levels of AST, ALT, ALP, GGT, TBIL, DBIL, CRP, and AMY in the standard biliary drainage group were significantly lower than those in the nasobiliary drainage group, with a statistically significant difference ($P < 0.05$). There were no statistically significant differences in serum levels of AST, ALT, ALP, GGT, TBIL, DBIL, CRP, and AMY between patients in the standard biliary drainage group and those in the nasobiliary drainage group ($P < 0.05$). Additionally, no statistically significant differences were found in two-by-two comparisons of WBC, Hb, and NEU indicators among the three patient groups (all $P > 0.05$) (Table 2).

Comparison of VAS scores between the three patient groups 24 hours before and after surgery

There was no statistically significant difference in VAS scores ($F = 0.077$, $P = 0.781$) 24 hours before surgery among the three patient groups. However, statistically significant differences in the VAS scores were observed among the three patient groups 24 hours after surgery ($F = 10.416$, $P < 0.001$) (Table 3). Preoperative covariates had no significant impact on the corresponding indicators in the three patient groups ($P = 0.781$).

VAS scores in all three groups significantly decreased 24 h after surgery compared to 24 hours before surgery ($P < 0.05$) (Table 3).

After adjusting for preoperative VAS scores, significant differences were found in VAS score changes between different drainage methods ($P < 0.001$). Post-hoc comparisons revealed that VAS scores in the modified pancreatic duct stent drainage group were significantly lower than those in the nasobiliary drainage group ($P < 0.05$). Similarly, VAS scores in the modified pancreatic duct stent drainage group were significantly lower than those in the standard biliary drainage

Table 1 The general clinical data of the three groups of patients were compared

	Modified pancreatic duct stent drainage group (*n* = 59)	Nasobiliary drainage group (*n* = 58)	Standard biliary drainage group (*n* = 58)	χ^2/F value	*P* value
Gender (male/female)	35 (59.32)/24 (40.68)	33 (56.90)/25 (43.10)	32 (55.17)/26 (44.83)	0.208	0.901
ASA classification (I/II/III)	22 (37.29)/28 (47.46)/9 (15.25)	11 (18.97)/36 (62.07)/11 (18.97)	16 (27.59)/32 (54.24)/10 (17.24)	4.887	0.299
The number of gallstones in the bile duct (1/2/3/≥ 4)	29 (49.15)/7 (11.86)/5 (8.47)/18 (30.51)	28 (48.28)/5 (8.62)/5 (8.62)/20 (34.48)	23 (39.66)/6 (10.34)/5 (8.62)/24 (41.38)	2	0.92
Age (year)	51.42 ± 15.14	52.00 ± 16.08	51.84 ± 15.84	0.021	0.979
BMI (kg/m^2)	23.34 ± 3.82	23.29 ± 3.67	23.16 ± 3.54	0.037	0.964
History of drinking (yes/no)	26 (44.07)/33 (55.93)	24 (41.38)/34 (58.62)	23 (39.66)/35 (60.34)	0.238	0.888
Time of onset before surgery (hours)	35.51 ± 3.25	35.94 ± 3.58	36.10 ± 4.33	0.389	0.678
Total hospital stay duration (days)	9.12 ± 4.34	10.62 ± 5.06	11.04 ± 5.13	2.536	0.082
Disease duration (month)	21.14 ± 4.28	22.04 ± 4.05	21.67 ± 3.94	0.715	0.491
Surgical duration (minutes)	61.04 ± 8.91	60.55 ± 6.42	60.07 ± 7.49	0.233	0.792
Diameter of the bile duct (cm)	1.34 ± 0.43	1.31 ± 0.48	1.38 ± 0.51	0.318	0.728
Stone diameter (cm)	0.86 ± 0.35	0.88 ± 0.36	0.91 ± 0.43	0.254	0.776

Results expressed as mean ± SD, or the number of patients and percentage (%). ASA: American Society of Anesthesiologists; BMI: Body mass index.

group (P = 0.033). Finally, the standard biliary drainage group had significantly lower VAS scores than the nasobiliary drainage group (P = 0.017) (Table 3).

Comparison of complication rates across the three patient groups

There was no statistically significant difference in complication rates among the three patient groups (P = 0.336) (Table 4).

DISCUSSION

Our study found that the modified pancreatic duct stent in ERCP treatment for patients with bile duct stones effectively reduced hepatocyte injury, improved liver function, alleviated inflammation and pain, enhanced patient comfort, and a higher level of safety compared to standard biliary drainage and nasobiliary drainage methods.

After performing ERCP lithotripsy, both domestic and international units commonly use ENBD and ERBD to reduce the risk of postoperative cholangitis and to lower the rate of postoperative pancreatitis[25-27]. Numerous randomized control trial studies have found no significant difference in bile drainage effectiveness or complications between biliary stents and ENBD[28-31], largely due to the fundamental principles of these two methods. ENBD, as an external drainage method, allows for the objective evaluation of drainage effectiveness through bile output volume and composition, facilitating better patient monitoring and management, particularly for thick bile. Furthermore, it reduces the risk of drainage tube blockage and insufficient drainage[32]. However, ENBD has its limitations. Its insertion involves a tube through the nasal passage, which may cause electrolyte imbalances and digestive issues if left in place for extended periods[33]. The tube can cause discomfort in the nasal and pharyngeal regions, local swelling, and hemorrhage, potentially increasing the risk of respiratory infections[33]. Meanwhile, ERBD, a newer drainage method, achieves bile drainage by inserting a biliary stent. It is generally more comfortable than ENBD. During the treatment of common bile duct stones, ERBD may facilitate stone reduction and improve postoperative outcomes by promoting gut nutrition[34]. Additionally, due to its stable design with cedar-like wings at the head end and the absence of side holes, the Christmas tree-shaped plastic stent enhances drainage patency and reduces the risk of retrograde infection. However, most plastic stents in the common bile duct cannot be dislodged independently and must be pulled out under endoscopy, increasing patients' discomfort and medical costs[35,36].

Cholelithiasis of the common bile duct can lead to obstruction of the hepatic bile duct circulation, causing liver cell injury and surrounding tissue damage, as evidenced by elevated liver function parameters, such as AST, ALT, ALP, GGT, TBIL, and DBIL[37,38]. Our study findings indicated that the postoperative levels of these markers were significantly lower in all three patient groups than preoperative values. However, both the modified pancreatic duct stent drainage group and the standard biliary drainage group had significantly lower levels of AST, ALT, ALP, GGT, TBIL, and DBIL than the nasobiliary drainage group. This indicates that all three drainage methods effectively alleviate intraductal pressure, facilitate bile flow, and reduce liver function impairment and bile metabolism abnormalities, thereby improving hepatobiliary function. Our results were consistent with Mangiavillano *et al*'s research[39], which showed that modified

Table 2 Comparison of laboratory indicators among three groups of patients, mean ± SD

	Modified pancreatic duct stent drainage group (*n* = 59)	Nasobiliary drainage group (*n* = 58)	Standard biliary drainage group (*n* = 58)	*F* value	*P* value	*P*1 value	*P*2 value	*P*3 value
AST (U/L)								
24 hours before the surgery	58.38 ± 18.49	55.71 ± 20.07	55.75 ± 20.84	0.217	0.642			
24 hours after the surgery	29.28 ± 3.47	48.64 ± 4.37	30.13 ± 3.88	449.671	< 0.001	< 0.001	< 0.001	0.240
ALT (U/L)								
24 hours before the surgery	85.36 ± 6.41	83.15 ± 6.74	84.28 ± 6.69	0.221	0.639			
24 hours after the surgery	35.44 ± 4.73	68.54 ± 5.58	36.49 ± 6.33	650.159	< 0.001	< 0.001	< 0.001	0.294
ALP (U/L)								
24 hours before the surgery	160.42 ± 35.48	159.45 ± 34.82	158.47 ± 31.82	1.153	0.284			
24 hours after the surgery	133.09 ± 33.21	153.14 ± 36.58	134.54 ± 31.25	6.390	0.002	0.002	0.003	0.837
GGT (U/L)								
24 hours before the surgery	383.45 ± 106.82	364.58 ± 119.42	322.84 ± 128.94	0.402	0.527			
24 hours after the surgery	252.64 ± 44.52	294.59 ± 51.60	255.52 ± 55.31	12.314	< 0.001	< 0.001	< 0.001	0.668
TBIL (mol/L)								
24 hours before the surgery	28.65 ± 6.77	28.94 ± 6.82	28.59 ± 5.82	1.603	0.207			
24 hours after the surgery	16.08 ± 3.38	24.36 ± 4.16	16.18 ± 3.67	94.115	< 0.001	< 0.001	< 0.001	0.878
DBIL (mol/L)								
24 hours before the surgery	12.53 ± 3.56	13.05 ± 3.81	13.34 ± 3.64	3.165	0.077			
24 hours after the surgery	8.59 ± 2.14	9.93 ± 2.42	8.96 ± 2.57	5.213	0.006	0.002	0.032	0.328
CRP (mg/L)								
24 hours before the surgery	104.58 ± 5.89	102.57 ± 6.68	101.53 ± 5.46	2.516	0.115			
24 hours after the surgery	83.65 ± 6.91	96.08 ± 7.04	84.53 ± 6.31	62.572	< 0.001	< 0.001	< 0.001	0.311
WBC ($\times 10^9$/L)								
24 hours before the surgery	11.28 ± 5.94	10.64 ± 4.58	10.53 ± 5.08	0.089	0.766			
24 hours after the surgery	9.51 ± 4.41	9.46 ± 5.02	9.48 ± 4.66	0.003	0.997	0.942	0.984	0.959
Hb (g/L)								
24 hours before the surgery	133.54 ± 20.19	134.48 ± 20.25	134.82 ± 20.72	2.171	0.143			
24 hours after the surgery	123.14 ± 19.58	124.15 ± 18.24	123.31 ± 18.94	0.043	0.958	0.796	0.805	0.992
NEU (%)								
24 hours before the surgery	0.78 ± 0.14	0.79 ± 0.13	0.78 ± 0.15	0.627	0.430			

24 hours after the surgery	0.73 ± 0.08	0.76 ± 0.09	0.74 ± 0.07	1.337	0.265	0.157	0.159	0.999
AMY (IU/L)								
24 hours before the surgery	281.26 ± 94.15	274.59 ± 93.08	268.42 ± 99.81	1.116	0.292			
24 hours after the surgery	121.46 ± 44.28	175.83 ± 46.82	127.43 ± 41.08	26.653	< 0.001	< 0.001	< 0.001	0.432

*P*1 represents the comparison between the modified pancreatic duct stent drainage group and nasobiliary drainage group. *P*2 represents the comparison between the nasobiliary drainage group and standard biliary drainage group. *P*3 represents the comparison between the standard biliary drainage group and modified pancreatic duct stent drainage group. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; CRP: C-reactive protein; WBC: White blood cells; Hb: Hemoglobin; NEU: Neutrophils; AMY: Amylase.

Table 3 Comparison of visual analogue scale scores among the three groups of patients, mean ± SD

	Modified pancreatic duct stent drainage group (*n* = 59)	Nasobiliary drainage group (*n* = 58)	Standard biliary drainage group (*n* = 58)	*F* value	*P* value	*P*1 value	*P*2 value	*P*3 value
VAS (point)								
24 hours before the surgery	6.25 ± 2.16	6.24 ± 2.45	6.26 ± 2.54	0.077	0.781			
24 hours after the surgery	4.36 ± 1.18	5.54 ± 1.24	4.92 ± 1.68	10.416	< 0.001	< 0.001	0.017	0.033

*P*1 represents the comparison between the modified pancreatic duct stent drainage group and nasobiliary drainage group. *P*2 represents the comparison between the nasobiliary drainage group and standard biliary drainage group. *P*3 represents the comparison between the standard biliary drainage group and modified pancreatic duct stent drainage group. VAS: Visual analogue scale.

Table 4 Comparison of complication occurrence in three groups of patients

	Modified pancreatic duct stent drainage group (*n* = 59)	Nasobiliary drainage group (*n* = 58)	Standard biliary drainage group (*n* = 58)	χ^2 value	*P* value
Complications	14 (23.73)	18 (31.03)	21 (36.21)	2.180	0.336
Pancreatitis	1 (1.69)	0 (0.00)	0 (0.00)		
Cholangitis	0 (0.00)	1 (1.72)	0 (0.00)		
Hemorrhage	0 (0.00)	2 (3.45)	2 (3.45)		
Perforation	1 (1.69)	0 (0.00)	1 (1.72)		
Wound infection	0 (0.00)	0 (0.00)	1 (1.72)		
Hyperamylasemia	12 (20.34)	15 (25.86)	17 (29.31)		
Death	0 (0.00)	0 (0.00)	0 (0.00)		

The number of patients and percentage (%).

pancreatic duct plastic stent drainage and standard biliary stent drainage were more effective in reducing liver cell injury and improving liver function in patients with common bile duct stones undergoing ERCP. This may be because placing the tube through the patient's nostril enables ENBD to reduce bile duct pressure and facilitates adequate drainage. However, prolonged nasal drainage could lead to bile loss and impair digestive function, hindering liver function recovery. Conversely, the biliary plastic stent placement aligns more closely with human anatomy, causing less discomfort to the throat and respiratory system. It maintains bile duct patency, effectively draining the pus and minimizing liver cell damage, which promotes recovery of liver function[39].

Elevated WBC is a traditional diagnostic indicator for bacterial infections; however, it is not a specific toxicological marker, as it can also be elevated due to granulocyte colony-stimulating factors, cytokines, and, in some inflammatory conditions, may even decrease[40]. NEU plays a crucial role in defending against bacteria by engulfing them, and an increased NEU level indicates bacterial infection and heightened inflammation[41]. CRP, an acute-phase response

protein, helps clear pathogens and necrotic cells from the body, aiding the immune response. CRP levels significantly rise in response to tissue injury, inflammation, or postsurgery[42]. AMY activity tests are clinically used to diagnose acute pancreatitis and can also assist in differentiating between other acute abdominal conditions, such as abdominal pain, rigidity, nausea, and vomiting[43]. Our study findings showed that after surgery, all three patient groups had significantly lower levels of WBC, Hb, and NEU than before surgery. CRP and AMY serum levels were significantly lower in the modified pancreatic duct stent drainage and standard biliary drainage groups than in the nasobiliary drainage group. This indicates that all groups experienced a trend toward improved inflammatory markers after cholecystectomy. However, compared to ENBD, both the modified pancreatic duct plastic stent and conventional biliary stent drainage were more effective in alleviating inflammation in patients undergoing ERCP for gallstone disease. This may be because biliary drainage induces autophagy in the intestinal mucosa, reducing the expression of inflammatory factors and thus mitigating inflammation[44]. Conversely, ENBD, with its prolonged nasal bile drainage, can lead to bile loss and intestinal mucosa damage, impairing autophagy and hindering the regulation of inflammatory factor expression.

Our study findings indicated that VAS scores in the modified pancreatic duct stent drainage group were significantly lower than those in the standard biliary drainage group, which had lower VAS scores than the nasobiliary drainage group. This indicates that pain symptoms were alleviated in all three patient groups with common bile duct stones following ECRP treatment. However, the modified pancreatic duct plastic stent offered more effective pain relief and improved comfort than the ENBD and standard biliary stents. This finding aligns with the findings of Longo *et al*[45]. The likely reason is that the modified pancreatic duct plastic stent better aligns with the human physiological structure, reducing nasopharynx stimulation associated with tube retention and minimizing discomfort related to the throat and respiratory system. The expert consensus on accelerated recovery after hepatobiliary and pancreatic surgery (2015 edition) highlights that the basic principle of accelerated recovery surgery is to reduce the stress response[46]. The earlier introduction of oral intake and fluids in the modified pancreatic duct stent group postsurgery aligns with this concept, promoting gastrointestinal function recovery, reducing intestinal stress, and minimizing fluid overload[47]. Additionally, the placement of the pancreatic stent effectively prevents bile reflux into the pancreas, preventing premature activation of pancreatic enzymes, enabling proper pancreatic fluid drainage, lowering intraductal pressure, and reducing pancreatic fluid infiltration into glandular tissue. This helps prevent self-digestion of the pancreas and alleviates patient pain[48].

Our study findings further showed no statistically significant difference in complication rates among the three groups, indicating that the three drainage methods had a similar impact on complications after ECRP for patients with common bile duct stones. This could be due to the modified pancreatic stent having the same diameter as the nasobiliary tube, enabling effective drainage and reducing the risk of early detachment, which could lead to drainage failure. Additionally, our study demonstrated that ERBD facilitated stone removal by causing the stent to move along with intestinal contractions, potentially breaking the stones into smaller pieces. Some stones are even fractured into multiple parts, making them easier to retrieve during subsequent procedures. Additionally, the single pigtail structure at the end of the modified 7Fr pancreatic stent helped prevent proximal displacement and reduced pressure on the intestinal mucosa, reducing the risk of biliary duct or duodenum perforations. By modifying the bile duct end to remove lateral wings, the study showed a higher likelihood of spontaneous detachment, a lower need for manual intervention, and sufficient drainage without the risk of prolonged stent retention, which could cause biliary obstruction, injury, or cholangitis[49].

Malpositioning and occlusion of the stent are common reasons for failed drainage following stent placement. The stent should be positioned within the dilated bile duct, ideally above the stone, with its proximal end extending at least 1 cm above the rim of the stone and its distal end located 1 cm beyond the papilla of Vater. Temporary narrowing of the biliary tract may occur during stent placement, which, while inevitable, is necessary for a smooth procedure. When selecting a biliary stent, it is important to consider factors such as effective drainage, preferably opting for a larger-diameter stent. In cases of recurrent jaundice or cholecystitis, the stent should be promptly removed and replaced with a new stent[50].

This study found that the modified pancreatic duct plastic stent effectively addresses the limitations of ENBD and standard biliary stent implantation, reducing the risk of displacement during drainage. This might be because it could better conform to the physiological structure of the human body. However, patients with this stent had a higher risk of cholangitis, potentially due to its reduced flexibility and the need for endoscopic resection.

This study has several limitations. First, it is a single-center study with a small sample size, a short follow-up period, and potential confounding factors. Second, the timing of laboratory assessments was not strictly controlled, and there was a lack of both short- and long-term data on patients' satisfaction with the drainage method. These limitations may introduce bias into the findings, highlighting the need for further multi-center, large-sample, prospective, and long-term follow-up studies to validate the results.

CONCLUSION

In conclusion, the use of modified pancreatic duct plastic stent drainage as an adjunct to post-ERCP treatment for choledochal stones effectively alleviated patients' pain, did not significantly affect the occurrence of postoperative complications, and demonstrated a higher safety profile. Compared to ENBD and standard biliary stenting, the modified pancreatic duct plastic stent drainage reduced liver cell injury, improved liver function parameters, alleviated inflammation and pain, enhanced comfort, accelerated recovery, and improved quality of life. Its clinical value is substantial, leading to its recommendation for broader application in ERCP treatment for patients with choledochal stones. We suggest that the modified pancreatic duct plastic stent be considered the first choice for post-ERCP drainage in these patients.

FOOTNOTES

Author contributions: Qian LJ, Xu C, Wang JR and Quan J contributed to the analysis and interpretation of data; Qian LJ and Xu C contributed to the writing, review, and/or revision of the manuscript. All authors contributed to the acquisition of data (acquired and managed patients) and final approved the manuscript. Qian LJ and Xu C contributed to the conception and design.

Institutional review board statement: The study protocol was approved by the Ethics Committee of Taizhou Fourth People 's 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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Retrospective Study

Control observation of different digestive tract reconstruction methods in total gastrectomy for gastric cancer

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Abstract

BACKGROUND

For patients with advanced gastric cancer, surgical resection remains the main treatment option. Total gastrectomy combined with radical resection of gastric cancer lesions and sentinel lymph nodes can significantly prolong the survival of patients. Digestive tract reconstruction after total gastrectomy is essential to maintain gastrointestinal function and optimize postoperative recovery. Therefore, it is very important to choose a suitable reconstruction method to improve the quality of life of total gastrectomy patients.

AIM

To evaluate the effects of different digestive tract reconstruction methods in gastric cancer patients undergoing total gastrectomy.

METHODS

This retrospective study included 172 patients who underwent total gastrectomy for gastric cancer at The First Hospital of Hebei Medical University for analysis. The patients were categorized into two groups: Group A, consisting of 90 patients who underwent modified Roux-en-Y gastrojejunostomy, and group B, consisting of 82 patients who underwent uncut Roux-en-Y gastrojejunostomy. The general patient characteristics, perioperative indicators, postoperative gastrointestinal

mucosal barrier function, nutritional status, immunological markers, and occurrence of complications were compared between the two groups.

RESULTS

Group A showed shorter digestive tract reconstruction time than group B ($P < 0.05$). On the first postoperative day, group A showed lower serum levels of D-lactate, diamine oxidase, and endotoxin than group B ($P < 0.05$). One month postoperatively, group A showed higher prognostic nutritional index, serum albumin, total protein, and body weight than group B ($P < 0.05$). One month postoperatively, the levels of cluster of differentiation (CD) 3 +, CD4 +, and CD8 + cells were not significantly different between two groups ($P > 0.05$). The complication rates were 10.00% in group A and 24.39% in group B; group A had a significantly lower complication rate than group B ($P < 0.05$).

CONCLUSION

Using modified Roux-en-Y gastrojejunostomy during total gastrectomy shortens the time required for gastrointestinal anastomosis, reduces surgery-induced gastrointestinal mucosal damage, and mitigates postoperative declines in nutritional status.

Key Words: Total gastrectomy; Digestive tract reconstruction; Gastric cancer; Gastrointestinal barrier; Immune function; Safety

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Core Tip: Total gastrectomy combined with radical resection of gastric cancer lesions and sentinel lymph nodes can significantly prolong the survival of patients. Postoperative digestive tract reconstruction is crucial to maintain gastrointestinal function and optimize postoperative recovery. This study found that the application of modified Roux-en-Y gastrojejunostomy in total gastrectomy shortened the gastrointestinal anastomosis time, reduced the gastrointestinal mucosal injury caused by the operation, and alleviated the decline in postoperative nutritional status. This approach also reduces the overall incidence of surgical complications.

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INTRODUCTION

Gastric cancer is a prevalent malignant tumor, with over one million new cases reported worldwide each year and approximately 800000 deaths attributed to the disease[1,2]. In clinical practice, chemotherapy and radiotherapy are commonly used as adjuvant treatments, often employed as neoadjuvant therapy before and after surgery, as well as for some advanced-stage patients who are unsuitable candidates for surgery. However, surgical resection remains the primary treatment modality[3]. Studies have shown that total gastrectomy with radical resection of gastric cancer lesions and sentinel lymph nodes can significantly prolong patient survival[4]. The method of digestive tract reconstruction following total gastrectomy is crucial for maintaining gastrointestinal function and optimizing postoperative recovery. Therefore, selecting an appropriate reconstruction method is crucial for improving the quality of life of patients undergoing total gastrectomy. Modified and uncut Roux-en-Y anastomoses are commonly used techniques for digestive tract reconstruction following this procedure. The modified Roux-en-Y anastomosis involves connecting the distal jejunum to the esophagus and joining the proximal jejunum to the distal jejunum to form a Y-shaped structure, which provides an enhanced anti-reflux effect[5]. Uncut Roux-en-Y anastomosis utilizes a special clamp on the Roux limb to keep it intact, creating a functional bypass that preserves normal intestinal motility and reduces the risk of blind loop syndrome[6]. This study investigated the impact of these two digestive tract reconstruction methods on gastrointestinal barrier function, immune function, and safety in patients with gastric cancer undergoing total gastrectomy, with the aim of providing a basis for optimizing surgical treatment strategies.

MATERIALS AND METHODS

General data

This retrospective study included 172 patients who underwent total gastrectomy for gastric cancer at The First Hospital of Hebei Medical University over the past four years. Based on the type of digestive tract reconstruction, the patients were categorized into two groups: Group A consisted of 90 patients who underwent modified Roux-en-Y gastrojejunostomy,

and group B consisted of 82 patients who underwent uncut Roux-en-Y gastrojejunostomy. The selection period for the patients was from April 2020 to April 2024. This study was approved by the Ethics Committee of The First Hospital of Hebei Medical University (approval No. 20220651). The inclusion and exclusion criteria for the study subjects are as follows.

Diagnostic criteria: The diagnostic criteria for gastric cancer patients included in the study were based on the standards outlined in the "2018 Guidelines for the Diagnosis and Treatment of Gastric Cancer"[7]. Patients were diagnosed using gastrointestinal endoscopy, and the diagnosis was further confirmed postoperatively through frozen pathological sections and immunohistochemical examinations.

Inclusion criteria: (1) Patient age range: 18-75 years; (2) Pathological staging of gastric cancer ≤ stage III, with no metastasis to distant organs or sites; (3) Preoperative performance status for gastric cancer patients assessed by the Karnofsky performance status score[8] ≥ 65, and Eastern Cooperative Oncology Group score[9] ≤ 2; (4) All patients were newly diagnosed with gastric cancer and had not received radiotherapy, chemotherapy, or immunotherapy before surgery; (5) Preoperative surgical safety assessment confirmed that patients had adequate coagulation, cardiovascular function, and respiratory function to tolerate surgery; and (6) Informed consent was obtained from all patients prior to surgery.

Exclusion criteria: (1) Patients with gastric patients and distant metastasis; (2) Patients with recurrent gastric cancer who previously underwent gastric cancer surgery; (3) Patients with stomach metastases from malignant tumors originating at other sites; (4) Patients with gastrointestinal perforation or extensive intra-abdominal infection; and (5) Patients with concomitant immunological diseases.

Surgery methods

Group A: Modified Roux-en-Y anastomosis. An appropriately sized stapler base was selected and positioned approximately 65 cm-70 cm from the ligament of Treitz. An opening was made in the jejunum, approximately 15 cm from the ligament of Treitz, to perform a side-to-side anastomosis between the proximal and distal jejunum. A circular stapler was used to perform a side-to-end anastomosis between the jejunum and lower esophagus. A linear stapler was then to transect and close the bowel at the window site. All the anastomoses were reinforced with interrupted silk sutures.

Group B: Uncut Roux-en-Y anastomosis. An appropriately sized stapler base was selected and placed at an opening in the jejunum, approximately 65 cm from the ligament of Treitz. The stapler was then inserted into the jejunum approximately 15 cm from the ligament of Treitz, and an opening was made proximally. A side-to-side anastomosis was performed in the jejunum approximately 8 cm from the ligament of Treitz. A circular stapler was then inserted proximally into the jejunum, and an end-to-side anastomosis was completed approximately 20 cm from the ligament of Treitz. All the anastomotic sites were reinforced with interrupted silk sutures.

Observation indicators and data collection

Statistical analyses were conducted on the baseline characteristics of the two groups of patients, including age, body mass index (BMI), sex, smoking and alcohol consumption status, tumor node metastasis (TNM) staging, lesion diameter, degree of tumor differentiation, and lymph node metastasis. Perioperative indicators, such as surgery duration, intraoperative blood loss, time to the first anal gas passage, and the average length of hospital stay, were also analyzed. Peripheral venous blood samples (3 mL) were collected preoperatively and three days postoperatively. The samples were centrifuged at 3000 rpm with a radius of 14 cm at room temperature for 10 minutes, and the upper serum layer was collected for further analysis. Indicators of gastrointestinal mucosal barrier function, including D-lactate, diamine oxidase (DAO), and endotoxin (ETX), were measured using enzyme-linked immunosorbent assay kits purchased from Shanghai Roche. Serum nutritional indicators such as serum albumin (ALB) and total protein (TP) were measured using an automatic biochemical analyzer (AU5800, Beckman Coulter), and the prognostic nutritional index (PNI) was calculated. Immunological indicators [cluster of differentiation (CD) 3 +, CD4 +, and CD8 +] were detected by flow cytometry using kits obtained from Shanghai Roche (Shanghai, China). The incidence of complications was recorded.

Statistical analysis

Data were analyzed using statistical product and service solutions 21.0. The levels of D-lactic acid, DAO and ETX measured in this study met the requirements for normal distribution and were described by mean ± SD. Comparisons between the two groups for these continuous variables were performed using a *t*-test. Categorical variables, such as gender, combined disease, TNM stage, were expressed as frequencies and percentages (%) to complete the statistical description, the statistical method between the groups using the χ^2 test; the statistical comparison criterion in the study was $P < 0.05$.

RESULTS

Analysis of the baseline characteristics' balance between the two groups

The baseline characteristics of patients in group A and group B were analyzed to assess balance, and no significant differences were found ($P > 0.05$). See Table 1.

Table 1 Analysis of the baseline characteristics' balance, mean ± SD/*n* (%)

General information	A group (*n* = 90)	B group (*n* = 82)	t/χ^2	*P* value
Age (years)	65.9 ± 8.1	63.8 ± 7.6	1.749	0.082
BMI (kg/m^2)	22.25 ± 2.20	22.45 ± 2.15	-0.602	0.548
Gender			0.268	0.604
Male	54 (60.00)	46 (56.1)		
Female	36 (40.00)	36 (43.9)		
Smoking			3.083	0.079
Yes	32 (35.56)	40 (48.78)		
No	58 (64.44)	42 (51.22)		
Tipple			1.995	0.158
Yes	28 (31.11)	34 (41.46)		
No	62 (68.89)	48 (58.54)		
TNM stage			2.892	0.089
I + II stage	61(67.78)	65 (79.27)		
III stage	29 (32.22)	17 (20.73)		
Focal diameter			2.2	0.138
≤ 3.0 cm	43 (47.78)	30 (36.59)		
> 3.0 cm	47 (52.22)	52 (63.41)		
Degree of tumor differentiation			2.393	0.122
High + medium differentiation	62 (68.89)	65 (79.27)		
Poorly differentiated	28 (31.11)	17 (20.73)		
Lymph node metastasis			3.123	0.077
Yes	38 (42.22)	24 (29.27)		
No	52 (57.78)	58 (70.73)		

BMI: Body mass index; TNM: Tumor node metastasis.

Comparison of surgical procedure indicators between the two groups of patients

The digestive tract reconstruction time for patients in group A was shorter than that for patients in group B ($P < 0.05$). However, there were no significant differences between group A and group B in terms of surgery duration, intraoperative blood loss, time to first anal gas passage, and average length of hospital stay ($P > 0.05$). See Table 2.

Comparison of gastrointestinal barrier function indicators between the two groups of patients

Preoperatively, the serum levels of D-lactate, DAO, and ETX were compared between group A and group B ($P > 0.05$). On the third day postoperatively, the serum levels of D-lactate, DAO, and ETX in both groups were significantly higher than their preoperative levels ($P < 0.05$). However, the serum levels of D-lactate, DAO, and ETX in group A were lower than those in group B on the third postoperative day ($P < 0.05$). See Table 3.

Comparison of nutritional indicators between the two groups of patients

Preoperatively, the PNI, serum ALB, TP, and body weight were compared between group A and group B ($P > 0.05$). One month postoperatively, the PNI, serum ALB, TP, and body weight in both groups were significantly lower than their preoperative levels ($P < 0.05$). However, the PNI and serum ALB levels in group A were higher than those in group B one month after surgery ($P < 0.05$). See Table 4.

Comparison of immunological indicators between the two groups of patients

Preoperatively, the levels of CD3 +, CD4 +, and CD8 + were compared between the groups ($P > 0.05$). One month postoperatively, both groups showed a significant decrease in CD3 + and CD4 + levels and a significant increase in CD8 + levels compared to their preoperative levels ($P < 0.05$). However, the CD3 +, CD4 +, and CD8 + levels were compared between group A and group B one month after surgery ($P > 0.05$). See Table 5.

Table 2 Comparison of surgical procedure indicators between the two groups of patients, mean ± SD

Group	*n*	Operation time (minutes)	Digestive tract reconstruction time (minutes)	Operative blood loss (mL)	Anal first exhaust time (hour)	Average length of stay (day)
A group	90	167.5 ± 14.3	24.8 ± 5.1	240.4 ± 48.1	46.9 ± 12.0	12.4 ± 2.4
B group	82	170.8 ± 17.2	27.0 ± 4.8	245.8 ± 43.7	45.1 ± 9.8	12.9 ± 2.8
t		-1.373	-2.906	-0.768	1.071	-1.261
P value		0.172	0.004	0.444	0.286	0.209

Table 3 Comparison of laboratory indicators related to gastrointestinal barrier function between the two groups, mean ± SD

Group	*n*	D-lactic acid (mg/L)		DAO (IU/L)		ETX (EU/mL)	
		Before operation	Postoperative 3 days	Before operation	Postoperative 3 days	Before operation	Postoperative 3 days
A group	90	2.43 ± 0.50	3.27 ± 0.61[a]	1.52 ± 0.40	2.11 ± 0.48[a]	0.41 ± 0.08	1.10 ± 0.21[a]
B group	82	2.30 ± 0.48	3.56 ± 0.67[a]	1.44 ± 0.45	2.24 ± 0.55[a]	0.43 ± 0.11	1.16 ± 0.24[a]
t		1.736	-2.971	1.234	-1.655	-1.372	-1.748
P value		0.084	0.003	0.219	0.100	0.172	0.082

[a]*P* < 0.05.

P values compared with the preoperative group. DAO: Diamine oxidase; ETX: Endotoxin.

Table 4 Comparison of nutritional indicators between the two groups of patients, mean ± SD

Group	*n*	PNI		ALB (g/L)	
		Before operation	One month after surgery	Before operation	One month after surgery
A group	90	55.91 ± 4.02	45.71 ± 4.00[a]	39.41 ± 3.44	35.10 ± 2.85[a]
B group	82	57.03 ± 5.18	43.31 ± 4.58[a]	40.42 ± 3.95	33.91 ± 3.02[a]
t		-1.592	3.668	-1.792	2.658
P value		0.113	0.000	0.075	0.009
Group	*n*	TP (g/L)		Body mass (kg)	
		Before operation	One month after surgery	Before operation	One month after surgery
A group	90	70.33 ± 4.03	64.62 ± 3.96[a]	64.31 ± 5.30	61.80 ± 4.71[a]
B group	82	71.40 ± 4.55	63.70 ± 4.03[a]	65.88 ± 5.51	60.73 ± 4.48[a]
t		-1.635	1.509	-1.904	1.523
P value		0.104	0.133	0.059	0.130

[a]*P* < 0.05.

P values compared with the preoperative group. PNI: Prognostic nutritional index; ALB: Albumin; TP: Total protein.

Comparison of complication rates between the two groups of patients

The complication rate in group A was 10.00%, while in group B, it was 24.39%. The complication rate in group A was considerably lower than in group B ($P < 0.05$). See Table 6.

DISCUSSION

Roux-en-Y anastomosis is a widely used method for digestive tract reconstruction after total gastrectomy. This surgical approach effectively preserves gastric function, is relatively straightforward to perform, and is associated with fewer postoperative complications, making it the preferred choice in clinical practice[10]. However, Roux-en-Y anastomosis

Table 5 Comparison of immunological indicators between the two groups of patients, mean ± SD

Group	*n*	CD3 + (%)		CD4 + (%)		CD8 + (%)	
		Before operation	One month after surgery	Before operation	One month after surgery	Before operation	One month after surgery
A group	90	63.20 ± 5.10	56.13 ± 4.77[a]	42.30 ± 4.46	38.37 ± 4.09[a]	24.42 ± 2.66	28.30 ± 2.96[a]
B group	82	64.51 ± 5.37	54.92 ± 4.40[a]	43.17 ± 4.85	37.45 ± 4.76[a]	25.07 ± 3.00	29.16 ± 3.05[a]
t		-1.641	1.724	-1.226	1.363	-1.506	-1.876
P value		0.103	0.087	0.222	0.175	0.134	0.062

[a]$P < 0.05$.

P values compared with the preoperative group. CD: Cluster of differentiation.

Table 6 Comparison of complication rates between the two groups of patients, *n* (%)

Group	*n*	Anastomotic fistula	Reflux esophagitis	Anastomotic ulcer	Diarrhea	Ileus	Complication rate
A group	90	2	2	0	4	1	9 (10.00)
B group	82	4	5	2	6	3	20 (24.39)
χ^2							6.339
P value							0.012

remains somewhat controversial, particularly regarding the preservation of the duodenum, the construction of an appropriate reservoir, and whether to transect the jejunum. A study by Chen *et al*[11] demonstrated that using four linear-cutting staplers in total gastrectomy can reduce the complexity of the surgical procedure. In a study by Yang *et al*[12], the use of a double-channel interposed jejunal digestive tract reconstruction method has been shown to improve postoperative nutritional status and quality of life in patients with gastric cancer. Similarly, the findings of Li *et al*[13] indicated that regulatory double-channel digestive tract reconstruction is superior to Billroth I and non-duodenal bypass methods in improving patient survival outcomes and reducing postoperative complications. This study compared the effectiveness and safety of the modified and uncut Roux-en-Y methods for gastrointestinal anastomosis following total gastrectomy.

A comparison of the general data of patients who underwent different anastomosis techniques showed no significant differences between the two groups in terms of age, BMI, sex, tumor characteristics, and lymph node metastasis. This minimized the influence of these factors on surgical outcomes and postoperative complications, thereby ensuring a better balance between the two groups. The modified Roux-en-Y method demonstrated a significant advantage in terms of surgical duration and complexity. The modified Roux-en-Y anastomosis requires only the placement of the stapler base and, after creating an opening, allows for a straightforward side-to-side anastomosis between the proximal and distal jejunum[14]. In contrast, uncut Roux-en-Y anastomosis involves multiple openings and anastomoses at 65 cm, 15 cm, 8 cm, and 20 cm from the ligament of Treitz, making the procedure more complex and significantly increasing the surgery time[15].

Moreover, a comparison of gastrointestinal barrier function on the third postoperative day showed that the modified Roux-en-Y digestive tract reconstruction method can lower the damage to gastrointestinal mucosal function caused by surgery. Surgical trauma activates the immune system and triggers the release of large quantities of inflammatory mediators[16]. These inflammatory mediators disrupt the integrity of the intestinal mucosal barrier, thereby promoting the activity of DAO[17]. Additionally, inflammatory mediators activate proteases that degrade tight junction proteins in the intestinal mucosa, increasing its permeability[18]. When the intestinal mucosal barrier function is compromised, the gut microbiota and their metabolic products can enter the bloodstream, leading to elevated levels of bacterial metabolites such as D-lactate and ETX in the serum. Adequate postoperative intestinal blood flow supply is one of the key factors in maintaining intestinal barrier function. Insufficient blood flow supply can lead to intestinal ischemia and barrier dysfunction, which in turn can trigger the invasion of bacteria and their metabolites. Improving the Roux-en-Y digestive tract reconstruction method can not only reduce stress reactions in the gastrointestinal tract, but also improve postoperative intestinal microcirculation, maintain the nutritional supply of intestinal blood flow, enhance the repair ability of intestinal epithelial cells, and reduce barrier damage. Reduce D-lactate, DAO, and ETX levels, and improve the occurrence of gastrointestinal symptoms such as diarrhea in patients.

In addition to serving as a temporary storage organ for food, the stomach is also responsible for the initial digestion of nutrients, including proteins and certain minerals. After total gastrectomy, food enters the small intestine directly without undergoing gastric digestion, affecting the initial breakdown and absorption of nutrients. Changes in postoperative dietary habits and appetite, as well as the occurrence of complications such as diarrhea and gastrointestinal dysfunction,

can affect the nutritional status of patients, resulting in varying degrees of reduction in the nutritional status of both groups of patients after surgery compared to before surgery. Nutritional status is closely related to postoperative wound healing, and insufficient nutrient intake can lead to slow wound healing. In this study, one month postoperatively, the PNI and serum ALB levels in group A were higher than those in group B, suggesting that the modified Roux-en-Y method for gastrointestinal anastomosis during total gastrectomy helps improve postoperative nutritional status. This may be because modified Roux-en-Y anastomosis reduces the systemic inflammatory response after surgery, thereby mitigating damage to the intestinal mucosal barrier, helping to restore the patient's normal physiological functions and improve their postoperative quality of life.

T cells are crucial components of the immune system. CD3 + T cells represent the total population of T cells, CD4 + T cells are helper T cells, and CD8 + T cells are cytotoxic T cells[19]. Surgical trauma can activate stress responses in the body, leading to a reduction in immune function[20]. The results of this study showed no significant differences in immune levels between patients one month after surgery who underwent different digestive tract anastomosis methods, indicating that the two surgical approaches have a similar impact on short-term postoperative immune recovery. However, the recovery of immune function may be a relatively slow process, and there are differences in the dynamic changes of immune cell subsets at different time points after surgery. In the early postoperative period, the number of CD4 + cells may decrease due to immune suppression. As the wound heals and the immune system recovers, the number of CD4 + cells will gradually increase, but the speed and degree of recovery will be affected by nutrition and anastomosis methods. The dynamic changes of these cell subpopulations exhibit different trends, and the first and second weeks after surgery are critical periods for immune system recovery, with significant changes in the number and function of immune cells. If immune indicators are only observed one month after surgery, a more critical window of immune response may be missed. Therefore, further exploration is needed to determine whether different anastomosis methods have an impact on postoperative immune recovery. Additionally, the study found that the modified Roux-en-Y method for gastrointestinal anastomosis helped reduce the occurrence of surgical complications. This technique is relatively straightforward, reduces the number of anastomoses and procedural complexity, and thereby lowers the risk of complications such as anastomotic leakage, reflux esophagitis, anastomotic ulcers, diarrhea, and intestinal obstruction, demonstrating good clinical safety.

Future research can combine data on surgical risk, recovery speed, and postoperative complications to comprehensively evaluate the relationship between surgical time and patient prognosis, while extending the monitoring time of immune function to observe the long-term trend of immune system recovery.

CONCLUSION

In conclusion, using the modified Roux-en-Y method for gastrointestinal anastomosis during total gastrectomy is beneficial for shortening the gastrointestinal anastomosis time, reducing gastrointestinal mucosal damage caused by surgery, and minimizing the decline in postoperative nutritional levels. Overall, this approach helps reduce the occurrence of surgical complications.

FOOTNOTES

Author contributions: Wei M, Jiang HB was the guarantor and designed the study; Wang YY, Shi YH, Han Z, participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Gao YC revised the article critically for important intellectual content.

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ORIGINAL ARTICLE

Retrospective Study

Short-term efficacy of laparoscopic radical resection for colorectal cancer and risk of unplanned reoperation after surgery

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Abstract

BACKGROUND

Surgery is the first choice of treatment for patients with colorectal cancer. Traditional open surgery imparts great damage to the body of the patient and can easily cause adverse stress reactions. With the continuous development of medical technology, laparoscopic minimally invasive surgery has shown great advantages for the treatment of patients with celiac disease.

AIM

To investigate the short-term efficacy of laparoscopic radical surgery and traditional laparotomy for the treatment of colorectal cancer, and the differences in the risk analysis of unplanned reoperation after operation.

METHODS

As the research subjects, this study selected 100 patients with colorectal cancer who received surgical treatment at the Yulin First Hospital from January 2018 to January 2022. Among them, 50 patients who underwent laparoscopic radical resection were selected as the research group and 50 patients who underwent traditional laparotomy were selected as the control group. Data pertaining to clinical indexes, gastrointestinal hormones, nutrition indexes, the levels of inflammatory factors, quality of life, Visual Analog Scale score, and the postoperative complications of the two groups of patients before and after treatment were collected, and the therapeutic effects in the two groups were analyzed and compared.

RESULTS

Compared with the control group, perioperative bleeding, peristalsis recovery time, and hospital stays were significantly shorter in the research group. After surgery, the levels of gastrin (GAS) and motilin (MTL) were decreased in both groups, and the fluctuation range of GAS and MTL observed in the research group was significantly lower than that recorded in the control group. The he-

moglobin (Hb) levels increased after surgery, and the level of Hb in the research group was significantly higher compared with the control group. After the operation, the expression levels of tumor necrosis factor-α, interleukin-6, and C-reactive protein and the total incidence of complications were significantly lower in the research group compared with the control group. One year after the operation, the quality of life of the two groups was greatly improved, with the quality of life in the research group being significantly better.

CONCLUSION
Laparoscopy was effective for colorectal surgery by reducing the occurrence of complications and inflammatory stress reaction; moreover, the quality of life of patients was significantly improved, which warrants further promotion.

Key Words: Colorectal cancer; Laparoscopic surgery; Laparotomy; Short-term efficacy; Complications

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Core Tip: With the advancement of medical technology, laparoscopic colorectal cancer surgery began to be widely used in the clinic. A retrospective analysis of patients with colorectal cancer suggests that, compared with traditional open surgery, laparoscopic surgery has advantages, such as a smaller incision, lower intraoperative blood loss, shorter hospital stays, and faster recovery. Concomitantly, laparoscopic surgery is less stimulating to the digestive tract of patients, has a definite effect, can reduce the occurrence of complications, reduces the inflammatory stress response, and significantly improves the quality of life of patients, which is worthy of further promotion and application.

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INTRODUCTION

Colorectal cancer is one of the most common malignant tumors of the digestive tract in clinical settings. Most of these patients are male and the fatality rate is high. The morbidity and mortality of colorectal cancer rank in third and fourth place among all malignant tumors, respectively, thus seriously threatening human life and health[1,2]. Epidemiological studies have shown that the gradual change in the lifestyle and diet structure of populations caused by social development has led to an increasing incidence of colorectal cancer[3,4]. The factors that induce colorectal cancer, such as low intake of dietary fiber, excessive intake of animal fat, genetic factors, and social factors, are complex and diverse[5,6]. The first choice of treatment for patients with colorectal cancer is surgery. Traditional laparotomy for colorectal cancer has many advantages, such as a clear and open field of vision, flexible and convenient operation, and complete tumor resection. However, because of its great damage to the patient's body, the immune system is seriously damaged, resulting in adverse stress reactions, causing great difficulties to the postoperative rehabilitation of patients[7-9]. With the development of clinical treatment methods, laparoscopic minimally invasive technology has begun to be widely used for the surgical treatment of patients with celiac disease[10]. Compared with laparotomy, laparoscopic colorectal cancer surgery can avoid the application limitations of traditional laparotomy, can minimize stress injury to patients, and has short-term advantages, such as a small incision, rapid recovery, and short hospital stays. Because it further shortens the rehabilitation process of patients, it has been widely used in the clinic[11-14]. To explore the application value of laparoscopic surgery and laparotomy in patients with colorectal cancer, this study collected the clinical data of 100 patients with colorectal cancer who were admitted to our hospital and performed a statistical analysis to compare the clinical effects of laparoscopic radical resection with those of laparotomy.

MATERIALS AND METHODS

General information

The data of patients with colorectal cancer who were admitted to the Yulin First Hospital from January 2018 to January 2022 were collected. A total of 100 patients were included in the study: (1) 50 patients who had undergone laparoscopic radical resection were included in the research group; and (2) 50 patients who had received traditional laparotomy were included in the control group.

Inclusion criteria: (1) All patients were diagnosed with colorectal cancer by color Doppler ultrasound or computed tomography before operation and pathological examination after operation; (2) All patients met the relevant diagnostic

Table 1 Comparison of general data between the two groups of patients

	Control group (*n* = 50)	Research group (*n* = 50)	*P* value
Gender (male/female)	27/23	30/20	0.5445
Age	57.36 ± 8.02	58.76 ± 7.23	0.8333
Tumor site			0.7205
Rectum	12	15	
Sigmoid colon	28	25	
Ascending colon	5	7	
Descending colon	5	3	
Tumor diameter	2.51 ± 0.48	2.42 ± 0.56	0.8429
TNM stage			0.8462
Stage I	18	17	
Stage II	26	25	
Stage III	6	8	

criteria for colorectal cancer included in the "clinical diagnosis and treatment guidelines tumor subvolume"; (3) No obvious invasion and distal metastasis were found before and during operation; and (4) All patients were in accordance with the relevant indications of operation and there were no contraindications for laparotomy in the open group and no contraindications in the laparoscopic group.

Exclusion criteria: (1) Patients with a history of tumor-related radiotherapy and chemotherapy; (2) Patients with inflammation, ascites, or severe adhesion in the abdominal cavity; (3) Patients with psychiatric disorders; and (4) Patients with severe underlying diseases, major organ failure, other malignant tumors, or coagulation disorders.

The basic data of the two groups are reported in Table 1. There was no significant difference in gender composition, average age, tumor site, tumor diameter, and tumor stage between the two groups ($P > 0.05$).

Surgical methods

Patients in the research group underwent laparoscopic radical surgery, whereas the patients in the control group underwent traditional laparotomy. The patients in both groups were placed on a liquid diet 24 hours before the operation and paid attention to maintaining a nutritional balance. The patients were treated with antibiotics and compound polyethylene glycol electrolyte powder at 24 hours before the operation, started fasting at 8 hours before the operation, were then placed on drinking fasting at 4 hours before the operation, and performed bladder emptying before the operation.

The specific surgical methods used to perform the laparoscopic radical surgery were as follows: The patients were placed in a low-level lithotomy position and were administered general anesthesia. A small incision of 2–4 cm was made in the left lower abdomen, to establish a CO_2 artificial pneumoperitoneum (the pneumoperitoneum pressure was maintained at 12–14 mmHg). The five-hole surgical path was selected for laparoscopy implantation in the patient, the lesion site and lymph node metastasis were confirmed with the assistance of laparoscopy, the length of the auxiliary incision was controlled within 5–6 cm, the primary lesion was removed under laparoscopy, the regional lymph nodes were cleared, *etc.*; finally, all incisions were sutured after the operation.

The specific surgical methods used to perform the traditional laparotomy were as follows: The patients were placed in a supine position and were administered general anesthesia. An incision with a length of 10–15 cm was made in the abdomen. The lesion was explored routinely, the specific surgical plan was selected according to the location and size of the tumor, the lesion was effectively separated from the surrounding tissue, and the incision was closely sutured after the operation.

The patients in the two groups were treated with routine fasting, gastrointestinal decompression, prevention and anti-infection, nutritional support, *etc.*

Observational indicators

The clinical indexes, gastrointestinal hormones, nutrition indexes, levels of inflammatory factors, quality of life, Visual Analog Scale (VAS) score, and postoperative complications were statistically analyzed in the two groups before and after the treatment.

The clinically related indicators included time of operation, perioperative bleeding, number of lymph nodes cleared, recovery time of intestinal peristalsis, first exhaust time, and length of hospital stay.

The gastrointestinal hormones included gastrin (GAS) and motilin (MTL), and the nutritional indicators included albumin (Alb) and hemoglobin (Hb).

The inflammatory factors included the tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). Fasting venous blood was collected (3 mL) before and 3 days after the operation. After routine centrifugation, the level of inflammatory factors in the serum was assessed using an automatic enzyme-labeled instrument (Thermo, United States) combined with an enzyme-linked immunosorbent assay kit (Huamei Bio, China).

The incidences of infection (including infection of the incisional wound, pulmonary infection, and urinary system infection), anastomotic fistula, uroschesis, ileus, and thrombus of the lower-extremity veins were statistically compared between the two groups.

Before and after the operation, the quality of life of the two groups of patients was evaluated using the Gastrointestinal Quality of Life Index (GIQLI). The total score on the GIQLI is 144, and a higher score indicates a higher quality of life for patients. The VAS was used to evaluate the pain degree of the patients at 1 day and 3 days after the operation, with the score ranging from 0 to 10 and a higher indicating a greater pain severity.

Statistical analysis

The propensity score matching method was used to reduce the differences in the baseline data between the two groups. The matched covariates included gender, age, tumor site, tumor diameter, clinical TNM stage, preoperative GAS level, preoperative MTL level, preoperative Alb level, preoperative Hb level, preoperative inflammatory factor level, and preoperative GIQLI score.

In this study, Statistical Package for the Social Sciences 24.0 was used to perform the statistical analysis. The test of the normality of the measurement data was performed in advance. The data that met the normal distribution were expressed as the mean ± SD, and a *t*-test was used for inter-group comparisons; in turn, the data that did not meet the normal distribution were expressed as the median and quartile [M (P_{25}, P_{75})], and the inter-group comparisons were carried out using the Shapiro–Wilks rank sum test. The χ^2 test was used for the inter-group comparison of categorical variables, which were expressed as a percentage (%) or constituent ratio. Finally, the risk factors that exhibited statistical significance were analyzed using a multivariate binary logistic regression analysis.

RESULTS

Analysis of the general clinical indexes of the patients

Compared with the control group, perioperative bleeding, the peristalsis recovery time, and hospital stays were significantly shorter in the research group ($P < 0.05$). In contrast, there was no significant difference in the time of operation, number of lymph nodes cleared, and first exhaust time between the two groups ($P > 0.05$) (Figure 1).

Analysis of gastrointestinal hormones and nutritional indexes

After the operation, the GAS and MTL levels were decreased in both groups, although the decrease in the GAS and MTL levels in the research group was smaller after the surgery ($P < 0.05$). The impact of laparoscopic radical surgery on the gastrointestinal tract was milder than that observed in the control group (Figure 2A and B). Conversely, the two treatment methods had no significant impact on the patients' Alb levels ($P > 0.05$); in turn, the Hb levels of the patients in the research group were significantly increased after the surgery ($P < 0.05$), whereas there was no significant change in the control group (Figure 2C and D). The therapeutic effect of laparoscopic radical surgery was superior to that of the control group.

Analysis of the levels of inflammatory factors before and after the operation

After the operation, the levels of inflammatory factors were significantly increased in both groups, although the levels of TNF-α, IL-6, and CRP were increased more significantly in the control group, with the differences between the two groups being statistically significant ($P < 0.05$) (Figure 3A–C).

Analysis of the incidence of postoperative complications

As shown in Figure 4A and B, several patients developed complications after the operation, such as wound infection, urinary system infection, and thrombus of the lower extremity veins. A total of 14 patients (28%) in the control group developed postoperative complications, and the total complication incidence was significantly higher than that detected in the research group (6%; $P < 0.05$) (Figure 4C).

Analysis of the quality of life and VAS score

The quality of life of the patients was greatly improved at 1 year after the operation, and the GIQLI score observed the research group was higher than that of the control group. The VAS score of the patients was slightly increased at 3 days after the surgery; however, the difference between the two groups was not significant ($P > 0.05$) (Figure 5).

DISCUSSION

Colorectal cancer occurs mostly in people aged 40–50 years and is mainly related to an irregular daily life and diet. The fatality rate of colorectal cancer is second only to that of lung cancer and liver cancer; thus, it brings great harm to the

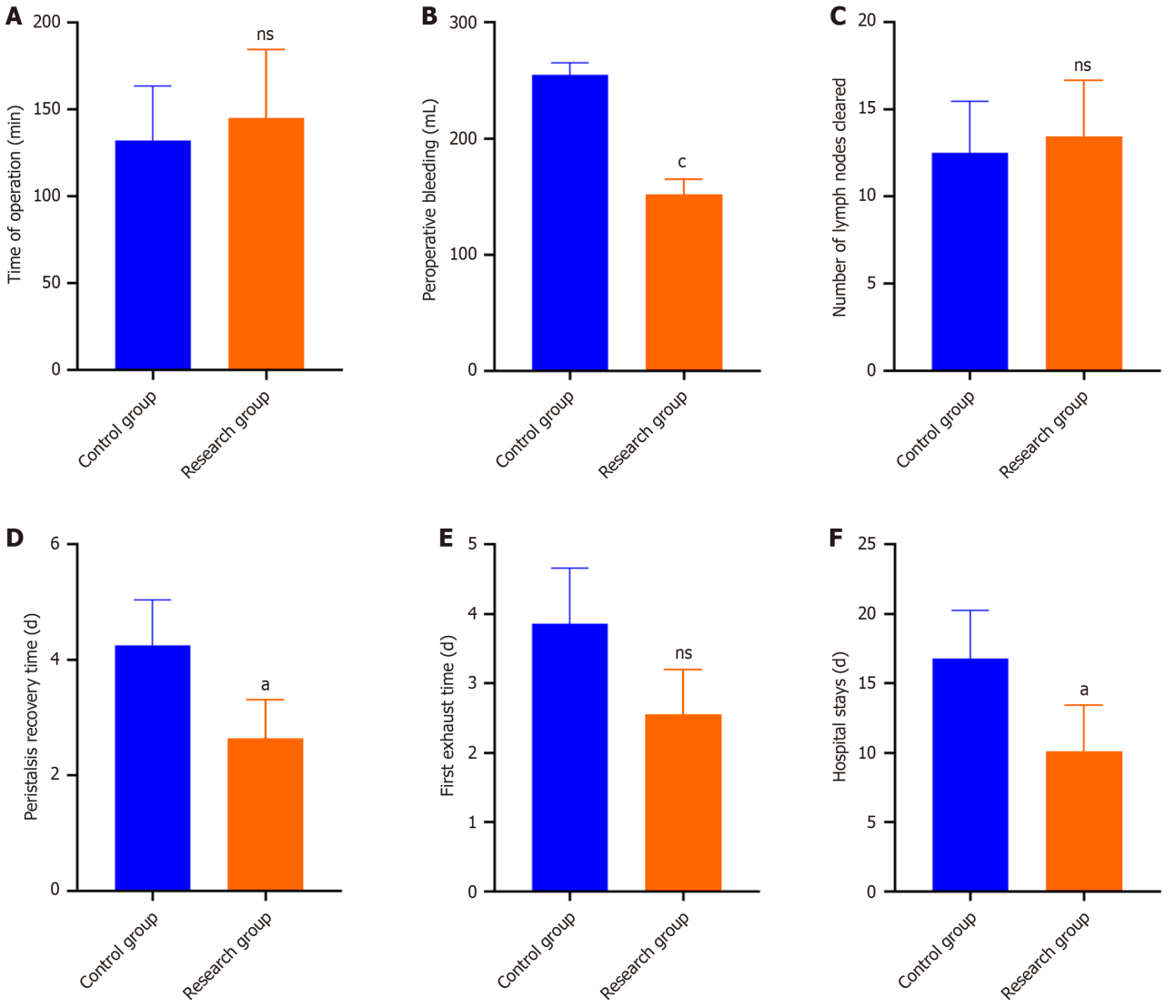


Figure 1 Analysis of general clinical indexes of patients in two groups (*n* = 100). A: Comparison of time of operation; B: Comparison of peroperative bleeding; C: Comparison of number of lymph nodes cleared; D: Comparison of peristalsis recovery time; E: Comparison of first exhaust time; F: Comparison of hospital stays. Compared with the control group, $^{ns}P > 0.05$, $^{a}P < 0.05$, $^{c}P < 0.001$.

health of patients[15,16]. Currently, the gold-standard treatment for colorectal cancer is surgery, which mainly includes routine laparotomy and laparoscopic-assisted surgery; the latter is minimally invasive and highly recognized in clinical settings[17]. This study collected the clinical data of patients with colorectal cancer and analyzed the differences in short-term efficacy, long-term survival, and quality of life between laparoscopic radical surgery and traditional laparotomy. Compared with the control group, perioperative bleeding, the peristalsis recovery time, and the length of hospital stays were significantly shortened in the research group, which may be because the laparoscopic high-definition field of vision can clearly show the anatomical structure of the tumor foci, can ensure the effect of vascular root ligation and cutting, and will not produce operation traction on the intestinal tissue near the tumor, while ensuring the effect of lymph node clearance, reducing perioperative bleeding, and accelerating the recovery of intestinal function after operation[18,19]. Relevant clinical studies have also shown that compared with traditional laparotomy, laparoscopic radical surgery affords a shorter operation time, lower intraoperative blood loss, and shorter hospital stay[20]. This fully indicates that laparoscopic radical surgery can shorten the operation time, reduce the trauma to patients, and promote patient recovery after surgery.

Previous studies have pointed out that GSA and MTL are both gastrointestinal hormones and that their levels are closely related to gastrointestinal function in patients with abdominal surgery[21]. In this study, the postoperative GAS and MTL levels decreased to varying degrees in both groups, indicating that the stress response caused by the surgical treatment affected the secretion of digestive-tract hormones. However, the decrease in the GAS and MTL levels observed after surgery in the research group was more modest than that detected in the control group, whereas the Hb level in the research group was significantly higher than that in the control group. These results show that, compared with traditional laparotomy, laparoscopic surgery has a weaker effect on the secretion of GSA, MTL, and Hb. Therefore, laparoscopic surgery can help protect the gastrointestinal function of patients and is more beneficial to their postoperative recovery, because this procedure pulls the digestive tract of the patients to a lesser extent than does laparotomy; thus, it will not

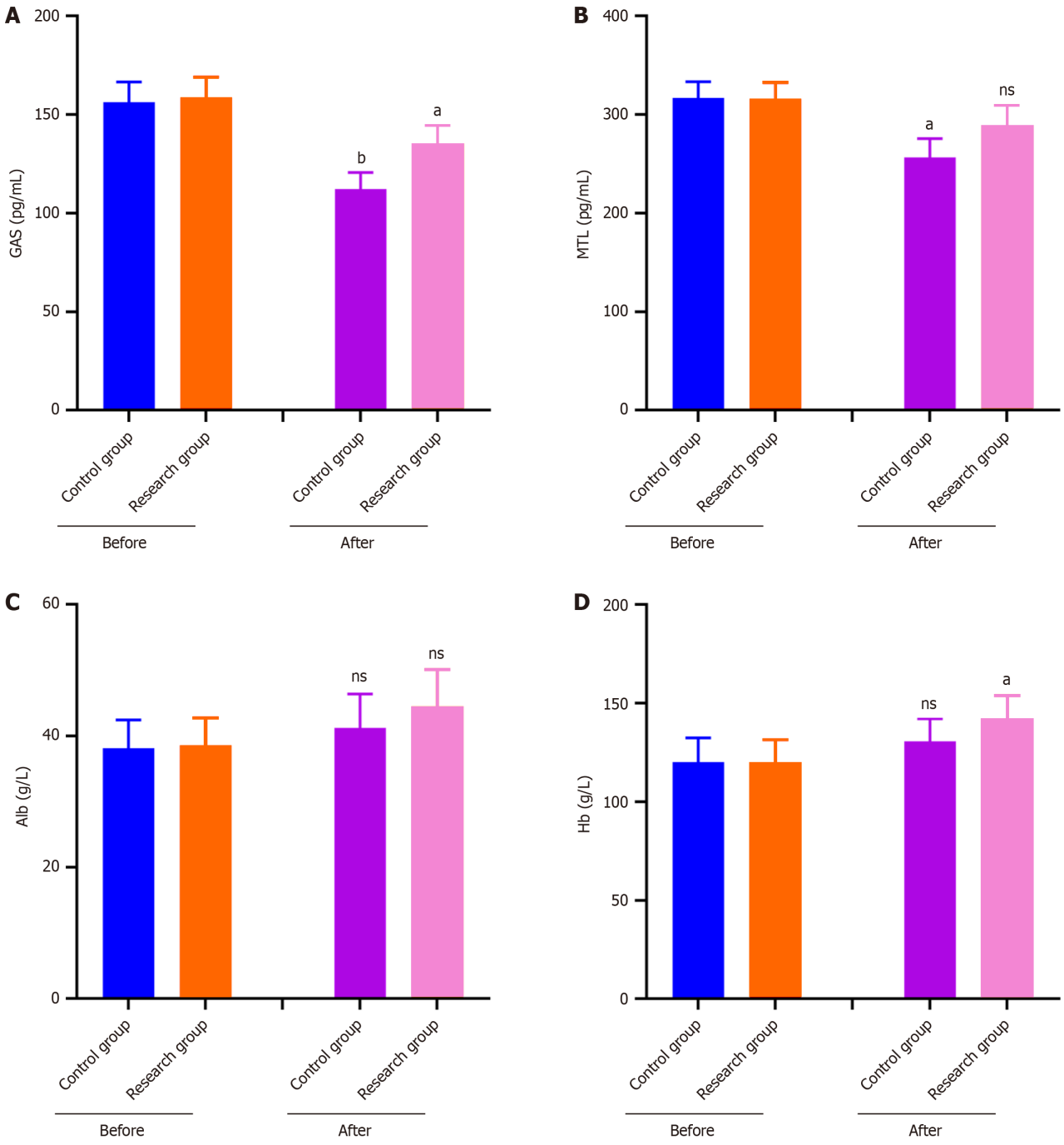


Figure 2 Analysis of gastrointestinal hormones and nutritional indexes of patients in two groups (n = 100). A: Comparison of gastrointestinal hormone gastrin level; B: Comparison of gastrointestinal hormone motilin level; C: Comparison of nutritional index albumin level; D: Comparison of nutritional index hemoglobin level. Compared with the before operation, $^{ns}P > 0.05$, $^{a}P < 0.05$, $^{b}P < 0.01$. Alb: Albumin; GAS: Gastrin; Hb: Hemoglobin; MTL: Motilin.

seriously affect the secretion of MTL and GAS. Moreover, it causes less stimulation to the nerves, blood vessels and intestines[22,23].

During the performance of abdominal surgery, and regardless of the surgical method that is selected, the organs and tissues in the abdominal cavity will be damaged to varying degrees, which may easily cause abnormal increases in the levels of inflammatory factors in the body, which, in severe cases, may lead to immune suppression[24]. TNF-α, CRP, and IL-6 are inflammation-related factors. Their levels can reflect the degree of the systemic inflammatory response in patients with colorectal cancer, and the effective control of the inflammatory response is key for the improvement of patient prognosis[25]. Here, the TNF-α, IL-6, and CRP levels in the research group were slightly increased after the operation, whereas the levels of inflammatory factors in the control group were increased more significantly. This indicates that laparoscopic surgery may minimize the damage to the patient's immune system and the stress response to surgery[26]. Concomitantly, compared with traditional laparotomy, laparoscopic radical surgery had a lower incidence of postoperative complications and significantly improved the postoperative quality of life of the patients. It is suggested that laparoscopic radical surgery offers greater advantages regarding postoperative recovery and the reduction of the occurrence of adverse reactions.

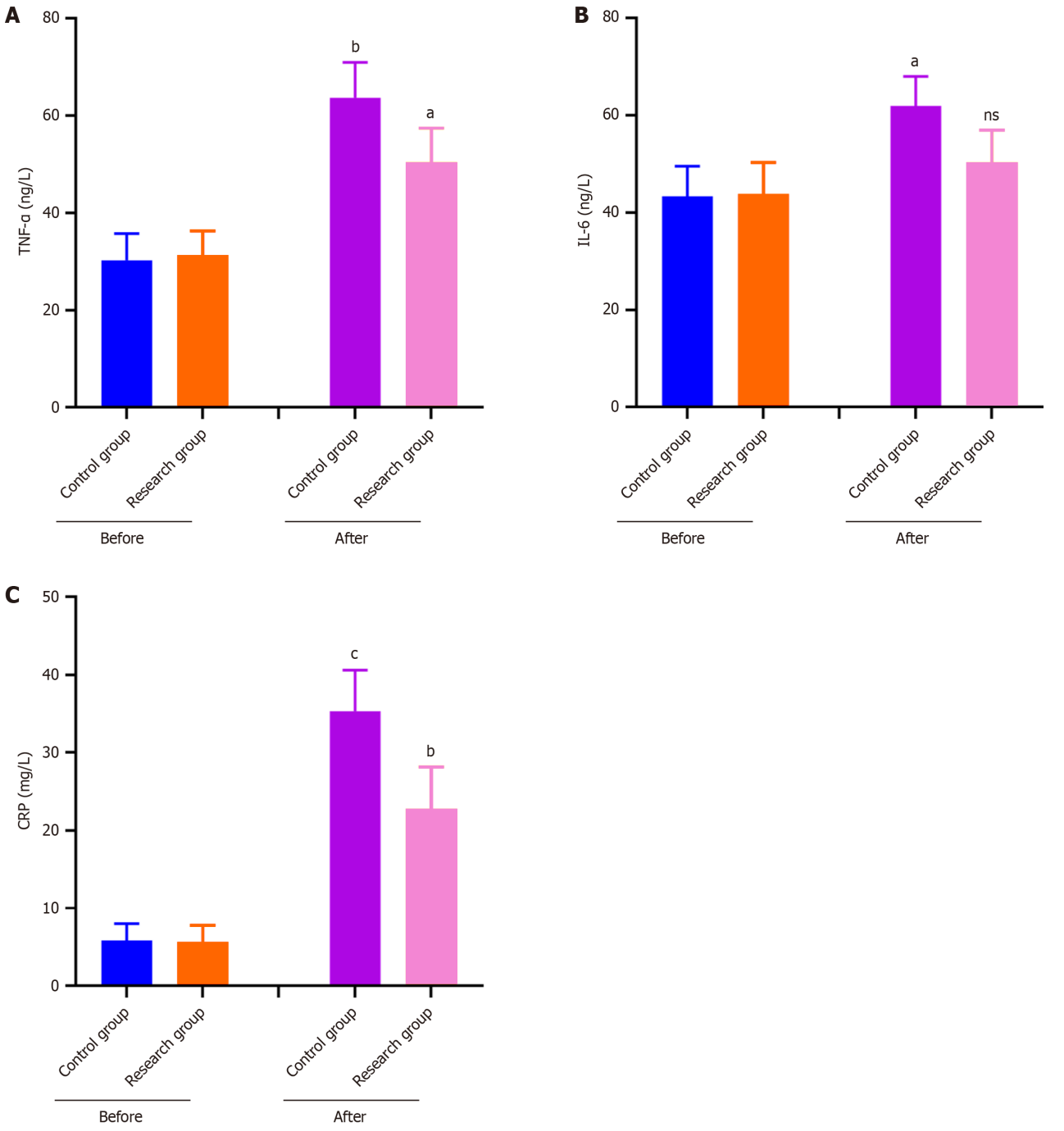


Figure 3 Analysis of the level of inflammatory factors before and after operation in two groups (*n* = 100). A: Comparison of the level of tumor necrosis factor-α before and after operation; B: Comparison of the level of interleukin-6 before and after operation; C: Comparison of the level of C-reactive protein before and after operation. Compared with the before operation, $^{ns}P > 0.05$, $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. CRP: C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.

CONCLUSION

In summary, compared with laparotomy, laparoscopic radical surgery for colorectal cancer can effectively reduce the risk of postoperative complications, reduce the inflammatory stress reaction of patients, and improve their quality of life after the operation, which is worthy of further application. However, this study was limited by its small sample size. Furthermore, this study only evaluated short-term prognostic indicators after surgery; therefore, the sample should be expanded through multiple channels to allow further long-term follow-up studies aimed at evaluating laparoscopic surgery regarding the long-term recovery of patients after surgery.

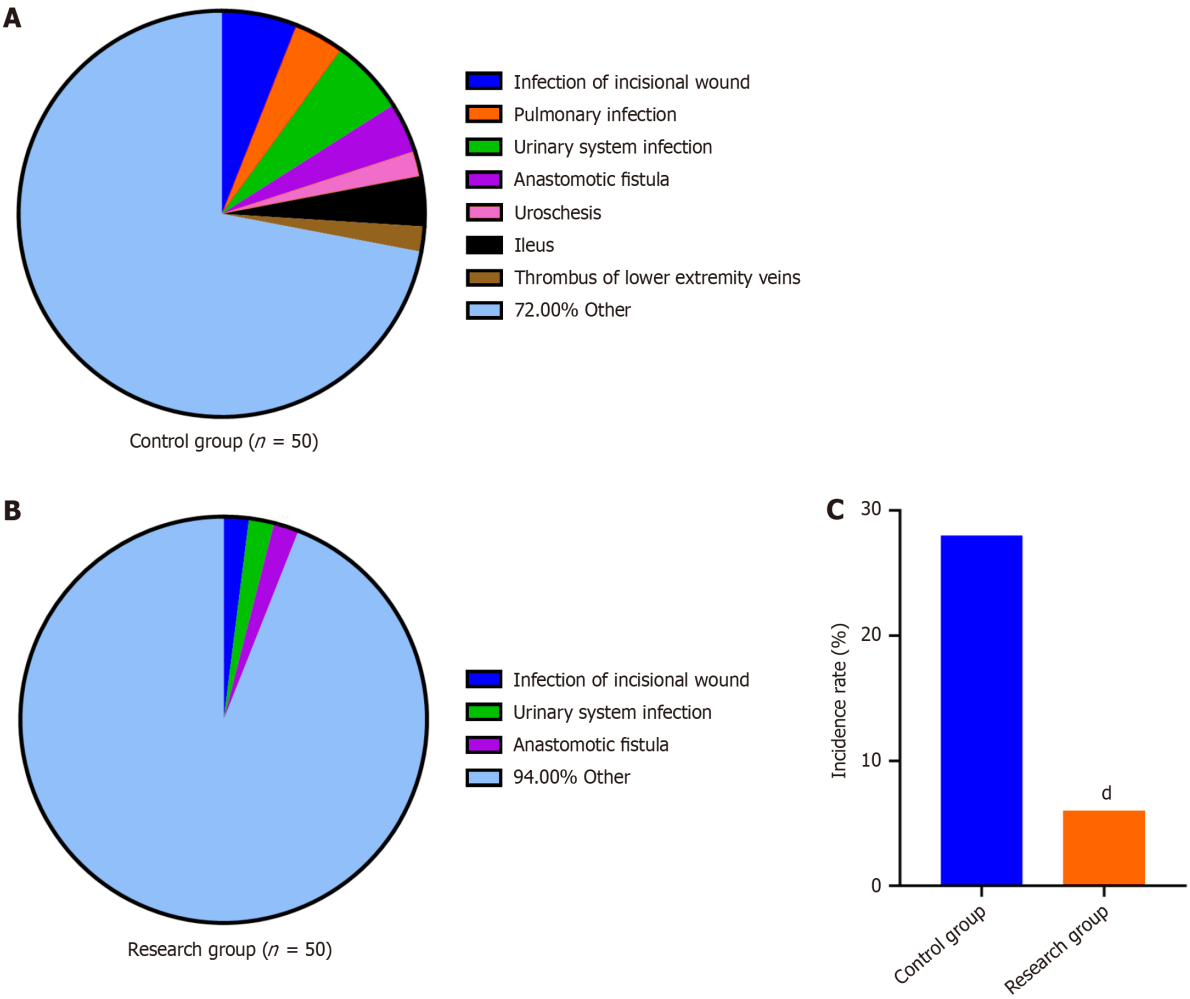


Figure 4 Analysis of the incidence of postoperative complications between the two groups (*n* = 100). A: The occurrence and probability distribution of postoperative complications in the control group; B: The occurrence and probability distribution of postoperative complications in the research group; C: The comparison of the incidence of postoperative complications between the two groups. [d]*P* < 0.0001.

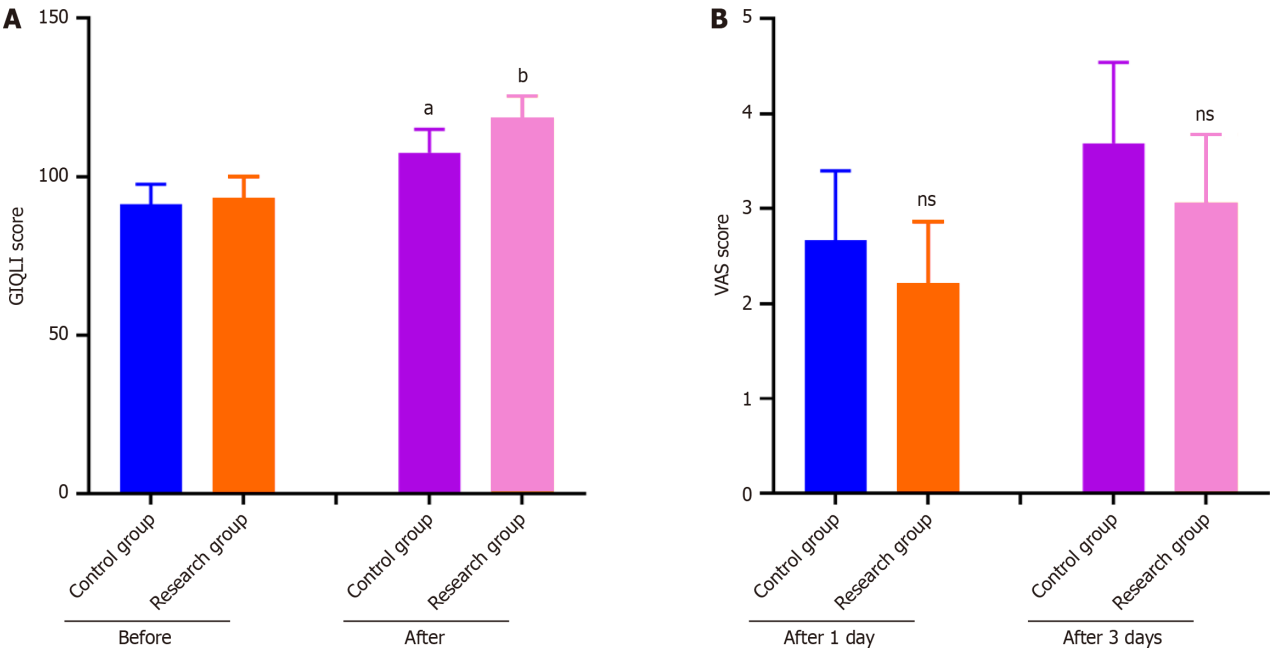


Figure 5 Analysis of Gastrointestinal Quality of Life Index score and Visual Analog Scale score before and after operation (*n* = 100). A:

Comparison of Gastrointestinal Quality of Life Index score before and after operation; B: Comparison of Visual Analog Scale scores at 1 day and 3 days after operation. $^{ns}P > 0.05$, $^{a}P < 0.05$, $^{b}P < 0.01$. GIQLI: Gastrointestinal Quality of Life Index; VAS: Visual Analog Scale.

FOOTNOTES

Author contributions: Li WB designed the research and wrote the first draft of the manuscript; Li WB and Gao JH contributed to conceiving the research and analyzing data, provided guidance for the research; Li WB, Li J, Yu W and Gao JH conducted the analysis; all authors reviewed and approved the final manuscript.

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

Informed consent statement: Patients did not need to provide informed consent for the study, as anonymous clinical data were used for analysis.

Conflict-of-interest statement: There is no conflict of interest.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors for bile leakage after laparoscopic common bile duct exploration in older patients with choledocholithiasis

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Abstract

BACKGROUND

At present, there are few studies on the risk factors for bile leakage after laparoscopic common bile duct exploration (LCBDE) for older patients with choledocholithiasis.

AIM

To identify the potential risk factors for bile leakage after LCBDE in older patients.

METHODS

A retrospective, single-center observational analysis was performed on patients aged ≥ 70 years with choledocholithiasis treated by LCBDE who were admitted to our center between January 2011 and August 2022. The included patients were divided into non-bile leakage and bile leakage groups. Risk factors were determined by analyzing the observation indicators.

RESULTS

Seventy older patients with choledocholithiasis who underwent LCBDE were included. Univariate analysis showed that positive culture of bile bacteria was a risk factor for bile leakage after LCBDE ($P < 0.05$). We further analyzed the bile bacteria, and univariate analysis showed that *Enterococcus faecalis* (*E. faecalis*) ($P < 0.05$) and *Pseudomonas aeruginosa* ($P < 0.05$) were associated with an increased risk of postoperative bile leakage in older patients ($P < 0.05$). Multivariate analysis

showed that *E. faecalis* was an independent risk factor for postoperative bile leakage in older patients ($P < 0.05$). The results of antibiotic sensitivity analysis showed that *E. faecalis* had 100% susceptibility to penicillin, ampicillin, linezolid, vancomycin, and furantoin.

CONCLUSION

E. faecalis-associated biliary tract infection is an independent risk factor for bile leakage after LCBDE in older patients with choledocholithiasis. We suggest coverage with antibiotics to which *E. faecalis* is sensitive.

Key Words: Bile leakage; Common bile duct stones; Older patients; Laparoscopic common bile duct exploration; *Enterococcus faecalis*; Antibiotic sensitivity

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Core Tip: This is a retrospective single-center observational study to investigate the potential risk factors for bile leakage after laparoscopic common bile duct exploration in elderly patients. *Enterococcus faecalis* (*E. faecalis*) is an independent risk factor for postoperative bile leakage in elderly patients. The results of drug sensitivity analysis showed that *E. faecalis* was fully sensitive to penicillin, ampicillin, linezolid, vancomycin, and furantoin. In elderly patients with choledocholithiasis who are at risk of postoperative bile leakage, we suggest covering sensitive drugs for *E. faecalis* in the empiric regimen of antibiotics.

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INTRODUCTION

According to the "2022 Revision of World Population Prospects", published by the United Nations (https://population.un.org/wpp/), the world's population is aging. One of the effects of an aging population is the increase in health problems of older people. The proportion of older patients requiring surgery is gradually increasing. However, increasing age itself is an important risk factor for postoperative morbidity and mortality[1]. Therefore, older patients are often considered to be at greater risk of surgical complications than younger patients.

Choledocholithiasis (common bile duct stones, CBDSs) is a common disease in clinical settings and occurs in 10%-20% of patients with gallstones, and the incidence of bile duct stones increases with age[2]. Patients with CBDSs often experience abdominal pain, fever, acute cholangitis, acute pancreatitis, obstructive jaundice, secondary biliary cirrhosis, and other symptoms. In serious cases, CBDSs may be fatal[3]. At present, there are two conventional methods for the treatment of CBDSs: Endoscopic retrograde cholangiopancreatography (ERCP)/endoscopic stone extraction and common bile duct exploration. Although ERCP treatment for CBDSs is widely favored[4], in some cases with large or multiple stones, ERCP often fails to remove the stones successfully[5-7], especially in older patients, in whom the failure rate is reported to be as high as 20%[8,9]. At this time, common bile duct exploration becomes the only effective method[10]. Laparoscopic common bile duct exploration (LCBDE) has the advantages of less trauma, faster recovery, and a similar postoperative complication rate compared with traditional open common bile duct exploration[11], and it has gradually replaced the open procedure. Bile leakage is a serious complication after LCBDE; in severe cases, bile leakage causes abdominal sepsis and may result in death[12]. The immune system and resistance of older patients are weaker, and they often have comorbid heart disease, cerebrovascular disease, pulmonary disease, diabetes mellitus, and other related diseases. Therefore, when bile leakage occurs in patients with CBDSs after surgery, the risk of death is increased[13-16]. Therefore, it is important to identify the potential risk factors for bile leakage after LCBDE in older patients and reduce the incidence of postoperative bile leakage.

MATERIALS AND METHODS

Patients

This was a retrospective analysis of older patients (≥ 70 years old) with CBDSs who were admitted to our center between January 2011 and August 2022. According to the treatment plan, the patients were divided into non-bile leakage and bile leakage groups after LCBDE. The study was approved by the Ethics Committee of our center (approval No. 2023029). Patient consent to review medical records was granted by the Institutional Ethics Committee. The handling of the patient data confidentiality strictly followed the rules set by the institution and complied with the Declaration of Helsinki.

Inclusion and exclusion criteria

Inclusion criteria: (1) Age ≥ 70 years; and (2) Patients were selected for LCBDE after they had a diagnosis of CBDSs confirmed by preoperative abdominal ultrasonography and/or magnetic resonance cholangiopancreatography (MRCP). All cases were confirmed to have no stone residue by imaging review (MRCP examination, T-tube cholangiography, indwelling nasobiliary cholangiography, *etc*.) after LCBDE.

Exclusion criteria: (1) Patients who were confirmed by preoperative MRCP or preoperative abdominal ultrasonography to have hepatolithiasis or congenital choledochal cysts; (2) Patients with complicated malignant tumors, such as those of the liver, gallbladder, bile duct, duodenal papilla, or pancreas; (3) Patients with common bile duct stenosis or intraoperative exploration of the lower end of the common bile duct obstruction; (4) Patients with structural variants of the bile duct; and (5) Patients with choledochojejunostomy or a history of choledochojejunostomy. We referred to studies on bile leakage published by the American Medical Association (2006) and the Society for Surgery of the Alimentary Tract (2008). The definition of bile leakage was as follows: Bile or fluid containing bile was detected in the drainage tube for > 3 days, and the volume of drainage containing bile was > 50 mL/day[17,18].

Selection of observation indicators

Observational indicators that were available were selected for statistical analysis, including sex, age, diabetes mellitus, hypertension, preoperative pulmonary disease, heart disease, cerebrovascular disease, American Society of Anesthesiologists score, viral hepatitis B, preoperative white blood cell count (< 10×10^9/L *vs* ≥ 10×10^9/L), percentage of neutrophils (< 70% *vs* ≥ 70%), hemoglobin (< 120 g/L *vs* ≥ 120 g/L), total bilirubin (< 34.2 mmol/L *vs* ≥ 34.2 mmol/L), direct bilirubin (< 17.1 mmol/L *vs* ≥ 17.1 mmol/L), indirect bilirubin (< 17.1 mmol/L *vs* ≥ 17.1 mmol/L), alanine transaminase (< 80 U/L *vs* ≥ 80 U/L), aspartate aminotransferase (< 70 U/L *vs* ≥ 70 U/L), alkaline phosphatase (< 100 U/L *vs* ≥ 100 U/L), γ-glutamyl transpeptidase (< 45 U/L *vs* ≥ 45 U/L), total bile acid (< 13 mmol/L *vs* ≥ 13 mmol/L), total cholesterol (< 5.7 mmol/L *vs* ≥ 5.7 mmol/L), high-density lipoprotein cholesterol (< 1.55 mmol/L *vs* ≥ 1.55 mmol/L), low-density lipoprotein cholesterol (< 3.36 mmol/L *vs* ≥ 3.36 mmol/L), amylase (< 133 U/L *vs* ≥ 133 U/L), total protein (< 65 g/L *vs* ≥ 65 g/L), albumin (< 35 g/L *vs* ≥ 35 g/L); associated cholecystectomy (yes *vs* no), stone position (bounded by the gallbladder duct: Upper and lower ends), number of stones (≤ 1 *vs* > 1), stone size (< 10 mm *vs* ≥ 10 mm), diameter of the common bile duct (< 10 mm *vs* ≥ 10 mm), operation mode (primary duct closure), T-tube drainage, primary duct closure + endoscopic nasobiliary drainage, abdominal surgery history (yes *vs* no), periampullary diverticula (yes *vs* no), postoperative fasting time (≤ 1 day *vs* > 1 day), and bacterial culture of bile (negative *vs* positive).

Bile bacterial cultures were derived from bile extracted after incision of the common bile duct. Samples were transferred to the microbiology department within 2 hours of collection and cultured according to the laboratory standard procedure. Bacterial identification and drug susceptibility tests were performed using the French Bio-Merieux ATB-Expression Automatic Bacterial Identification and Drug Susceptibility Test instrument. The results were evaluated based on the 2010 recommendations of the American Society for Clinical Laboratory Standardization Antimicrobial Susceptibility Test Standards.

Statistical analysis

SPSS 20.0 was used to analyze the data of the observation indicators (potential risk factors) one by one. For pairwise comparisons of groups, we used the χ^2 test or Fisher's exact test for categorical variables and Student's t test for quantitative variables. Multivariable logistic regression was conducted to determine the independent risk factors. $P < 0.05$ was considered statistically significant.

RESULTS

Seventy older patients with CBDS underwent LCBDE. There were 58 patients without bile leakage and 12 with bile leakage. There were 15 patients (21.4%) with diabetes mellitus, 42 (60%) with hypertension, 22 (31.4%) with pulmonary disease, 12 (17.4%) with heart disease, and 12 with cerebrovascular disease. There were no significant differences in demographic data or clinical characteristics between the two groups (Table 1). Univariate analysis was performed on the observed indicators. Positive culture of bile bacteria was identified to be a risk factor for bile leakage after LCBDE in older patients with CBDS ($P < 0.05$) (Table 2). This study had one limitation: Because of its retrospective nature, missing data were an inherent problem (missing data are marked with 1) (Table 2). Because they were missing at random, and the number of missing data points was small, we used the multiple imputation method to fill in the missing data, so the results are still considered reliable[19].

We subdivided the results into bile bacteria in patients without bile leakage and bile bacteria in patients with bile leakage (Table 3). The distribution of bile bacteria in patients with bile leakage was different from that in patients without. To compare the effects of different species of bile bacteria on risk factors for bile leakage after LCBDE in older patients with CBDS, we conducted further analysis. Univariate analysis showed that *Enterococcus faecalis* (*E. faecalis*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) were associated with an increased risk of postoperative bile leakage ($P < 0.05$). Multivariate analysis showed that *E. faecalis* was an independent risk factor for postoperative bile leakage in older patients with CBDS ($P < 0.05$) (Table 4). According to the results of the drug sensitivity analysis, the bacteria were divided into susceptible, intermediate, and resistant groups. The results showed that *E. faecalis* was fully susceptible to ampicillin, penicillin, vancomycin, linezolid, and furantoin (Figure 1).

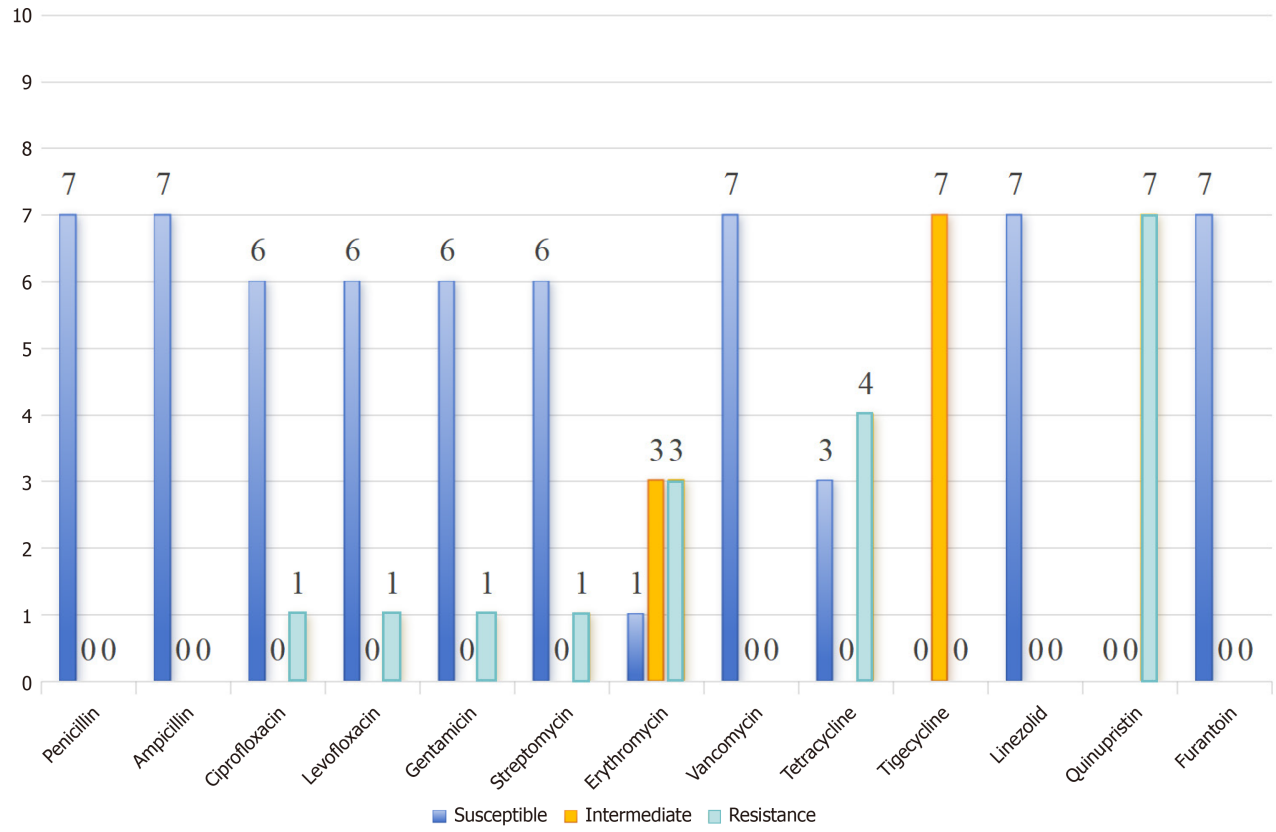


Figure 1 Drug sensitivity analysis of *Enterococcus faecalis*.

DISCUSSION

According to Goldman's index of cardiac risk, it was often believed that patients over the age of 70 years had a higher risk of surgery. However, with the development of medical technology, LCBDE is currently considered a safe and effective treatment for older patients with CBDSs[20,21]. Bile leakage is a serious complication after LCBDE, and the probability of occurrence is 3.8%-15.3%[22-24]. Some studies have shown that the mortality rate of postoperative bile leakage can be as high as 10%[25,26], especially in older patients, as the immune system and resistance of elderly patients are weaker, and they often have comorbid heart disease, cerebrovascular disease, pulmonary disease, diabetes mellitus, and other related diseases. When bile leakage occurs in elderly patients with CBDS after surgery, the risk of death will be increased[13-16]. Although most cases of bile leakage can be improved after conservative treatment or ERCP stent drainage, it costs patients much time and money and causes pain. In terms of the long-term prognosis, bile leakage can lead to an increase in the probability of malignant tumors of the bile duct[27]. Therefore, it is important to reduce the occurrence of bile leakage as much as possible.

At present, there are few studies on the risk factors for bile leakage after LCBDE for older patients with CBDSs, so there is currently no effective clinical guidance available. The results of this study show that positive culture of bile bacteria was a risk factor for bile leakage after LCBDE in older patients with CBDSs. It has been found that positive cultures of bile bacteria can lead to an increased risk of postoperative wound infection, and bacterial cultures taken from the infectious site were similar to the bile flora of the patients[28]. Although there has been no study on the mechanism of bacterial infection and bile leakage, according to studies on bacterial infection and colorectal anastomotic leakage, after bacterial colonization around the anastomosis site, *E. faecalis* and *P. aeruginosa* can release collagenase[29-32]; however, collagen plays an important role in the healing of the anastomosis. Therefore, we speculate that this may be because bile-containing bacteria flow out of the bile duct after incision of the duct, causing bacterial colonization around the incision site. By releasing collagenase, the bacteria affect the healing of the bile duct incision, eventually leading to bile leakage.

It is generally considered that bile is sterile, and a positive bile culture often indicates acute or chronic cholangitis[33]. It is a common cause of abdominal infection and life-threatening conditions, and mortality rates can be as high as 9%-12% in older patients[34]. In this study, a total of 14 species of bacteria were found in bile culture, but no fungal infections were found. Among 14 species of bacteria identified, Gram-negative bacteria accounted for 47.4%, and Gram-positive bacteria accounted for 52.6%. The top five bile bacteria were *E. faecalis* (7 strains, 18.9%), *Escherichia coli* (6 strains, 16.2%), *Enterococcus faecium* (5 strains, 13.5%), *Klebsiella pneumoniae* (4 strains, 10.8%), and *Enterococcus gallinarum* (4 strains, 10.8%), which is similar to other studies[28,35,36]. We found that *E. faecalis* was an independent risk factor for bile leakage after LCBDE in older patients with CBDSs. Although our univariate analysis showed that *P. aeruginosa* was also a risk factor for bile leakage after LCBDE in older patients with CBDSs, because the number was small, multivariate analysis could not be performed, which was a limitation of this study.

Table 1 Demographic data and clinical characteristics of older patients with common bile duct stones

Characteristic	Non-bile leakage	Bile leakage	*P* value
Sex			
Male	26	5	1.000
Female	32	7	-
Age (years), mean ± SD	77.10 ± 5.483	79.09 ± 6.788	0.278
Diabetes mellitus			
Yes	10	5	0.136
No	48	7	-
Hypertension			
Yes	33	9	0.400
No	25	3	-
Pulmonary disease			
Yes	16	6	0.128
No	42	6	-
Heart disease			
Yes	9	3	0.709
No	49	9	-
Cerebrovascular disease			
Yes	9	3	0.709
No	49	9	-
ASA score			
II	44	9	0.433
III	13	2	-
IV	1	1	-

ASA: American Society of Anesthesiologists.

We conducted antibiotic sensitivity analysis on *E. faecalis* and found that it was 100% susceptible to penicillin, ampicillin, linezolid, vancomycin, and furantoin, and > 85% susceptible to ciprofloxacin, levofloxacin, gentamicin, and streptomycin. This is similar to other studies[37-39]. Although there are many studies on bile microorganisms and drug sensitivity analysis, because of the worldwide increase in multidrug-resistant bacteria, the choice of antibiotic treatment options remains a challenge for clinicians. Antibiotic selection and timely use are important for improving the prognosis of patients[40]. Studies have found that inadequate initial antimicrobial therapy is associated with increased 30-day mortality in patients with bacterial cholangitis[41-43]. The results of bacterial susceptibility analysis of bile culture in this center were obtained on days 3-4 after surgery. However, some of the 12 patients developed bile leakage within 3 days after surgery; therefore, the correct empiric antibiotic regimen before and after surgery is important. Some studies have found that *E. faecalis* is associated with the occurrence of postoperative complications of biliary tract diseases[28,44], and Nitzan *et al*[36] found that deaths in patients with acute cholangitis may be related to the empiric regimen not covering *Enterococcus* and *Candida* species. Therefore, we suggest coverage with antibiotics to which *E. faecalis* is sensitive in the empiric regimen.

CONCLUSION

We found that *E. faecalis*-associated biliary tract infection is an independent risk factor for bile leakage after LCBDE in older patients with CBDSs. *E. faecalis* was 100% susceptible to penicillin, ampicillin, linezolid, vancomycin, and furantoin, and > 85% susceptible to ciprofloxacin, levofloxacin, gentamicin, and streptomycin. Therefore, for patients with cholangitis, we suggest coverage with antibiotics to which *E. faecalis* is sensitive in the empiric regimen, to reduce the incidence of postoperative bile leakage in older patients with CBDSs.

Table 2 Analysis of factors related to bile leakage after laparoscopic common bile duct exploration

Characteristic	Non-bile leakage	Bile leakage	*P* value
Sex			
Male	26	5	1.000
Female	32	7	-
Age (years), mean ± SD	77.10 ± 5.483	79.09 ± 6.788	0.278
Viral hepatitis B			
Yes	2	1	1.000
No	56	11	-
Diabetes mellitus			
Yes	10	5	0.136
No	48	7	-
Hypertension			
Yes	33	9	0.400
No	25	3	-
White blood cell count			
< 10×10^9/L	51	12	0.343
≥ 10×10^9/L	7	0	-
Percentage of neutrophils			
< 70%	32	7	1.000
≥ 70%	26	5	-
Hemoglobin			
< 120 g/L	31	9	0.292
≥ 120 g/L	27	3	-
Total bilirubin			
< 34.2 μmol/L	41	6	0.165
≥ 34.2 μmol/L	17	6	-
Direct bilirubin			
< 17.1 μmol/L	39	6	0.256
≥ 17.1 μmol/L	19	6	-
Indirect bilirubin			
< 17.1 μmol/L	43	9	1.000
≥ 17.1 μmol/L	15	3	-
Alanine transaminase			
< 80 U/L	29	8	0.462
≥ 80 U/L	29	4	-
Aspartate aminotransferase			
< 70 U/L	39	8	1.000
≥ 70 U/L	19	4	-
Alkaline phosphatase			
< 100 U/L	12	2	1.000
≥ 100 U/L	46	10	-
γ-glutamyl transpeptidase			

< 45 U/L	5	2	0.751
≥ 45 U/L	53	10	-
Total bile acid			
< 13 μmol/L	38	6	0.311
≥ 13 μmol/L	20	6	-
Total cholesterol[1]			
< 5.7 mmol/L	49	12	0.341
≥ 5.7 mmol/L	9	0	-
High-density lipoprotein cholesterol[1]			
< 1.55 mmol/L	45	11	0.476
≥ 1.55 mmol/L	13	1	-
Low-density lipoprotein cholesterol[1]			
< 3.36 mmol/L	46	11	0.552
≥ 3.36 mmol/L	12	1	-
Amylase			
< 133 U/L	50	10	1.000
≥ 133 U/L	8	2	-
Total protein			
< 65 g/L	36	9	0.603
≥ 65 g/L	22	3	-
Albumin			
< 35 g/L	28	6	0.913
≥ 35 g/L	30	6	-
Associated cholecystectomy			
Yes	57	12	1.000
No	1	0	-
Stone position			
Upper	11	4	0.473
Lower ends	47	8	-
Number of stones			
≤ 1	23	4	0.933
> 1	35	8	-
Stone size			
< 10 mm	15	5	0.452
≥ 10 mm	43	7	-
Diameter of CBDSs			
< 10 mm	6	2	0.898
≥ 10 mm	52	10	-
Operation mode			
PDC	32	4	0.345
T-tube drainage	21	7	-
PDC + ENBD	5	1	-
Abdominal surgery history			

Yes	14	4	0.764
No	44	8	-
Periampullary diverticula			
Yes	4	2	0.593
No	54	10	-
Postoperative fasting time			
≤ 1 day	33	9	0.400
> 1 day	25	3	-
Bacterial culture of bile[1]			
Negative	26	1	< 0.05
Positive	32	11	-

[1]Missing data are marked.
CBDSs: Common bile duct stones; ENBD: Endoscopic nasobiliary drainage; PDC: Primary duct closure.

Table 3 Distribution of bile bacteria after laparoscopic common bile duct exploration in older patients with common bile duct stones

Bile bacteria	Non-bile leakage	Bile leakage
Enterococcus faecalis	3	4
Escherichia coli	5	1
Enterococcus faecium	4	1
Klebsiella pneumoniae	2	2
Enterococcus gallinarum	3	1
Enterobacter cloacae	2	1
Pseudomonas aeruginosa	0	2
Aeromonas caviae	0	1
Staphylococcus aureus	1	0
Staphylococcus hemolyticus	1	0
Actinomyces israeli	1	0
Enterococcus hirae	0	1
Morganella morganii	1	0
Klebsiella oxytoca	1	0
Polymicrobial	5	3

Table 4 Effect of different bile culture bacterial types on bile leakage in older patients with common bile duct stones after laparoscopic common bile duct exploration

Bacteria	Non-bile leakage	Bile leakage	*P* value	Logistic regression analysis (*P* value, OR, 95%CI)
Enterococcus faecalis				
Yes	3	4	< 0.05	< 0.05, 7.857, 1.321-46.438
No	53	7	-	-
Escherichia coli				
Yes	5	1	1.000	-
No	43	10	-	-

Enterococcus faecium				
Yes	4	1	1.000	-
No	44	10	-	-
Klebsiella pneumoniae				
Yes	2	2	0.316	-
No	46	9	-	-
Enterococcus gallinarum				
Yes	3	1	1.000	-
No	45	10	-	-
Pseudomonas aeruginosa[1]				
Yes	0	2	< 0.05	NA, NA, NA
No	48	9	-	-
Aeromonas caviae				
Yes	0	1	0.186	-
No	48	10	-	-
Monomicrobia	41	8	0.356	-
Polymicrobial	5	3	-	-

[1]Test not performed due to few events and no events in one arm.
NA: Not available; OR: Odds ratio; CI: Confidence interval.

FOOTNOTES

Author contributions: Xiong RF, Lu SS, and Wu ZM were responsible for the conception and design of the study and drafting the article; Xiong RF and Lu SS contributed equally to this article as co-first authors; Xiong RF, Lu SS, Wu ZM, and Huang HJ contributed to the data analysis and interpretation; Huang HJ contributed to acquisition of the data; Xiao T was responsible for revising the manuscript critically for important intellectual content, and final approval of the version to be submitted; and all authors thoroughly reviewed and endorsed the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Nomogram for predicting myocardial injury in pediatric patients undergoing living donor liver transplantation for biliary atresia

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Abstract

BACKGROUND

Myocardial injury is common during liver transplantation and is associated with poor outcomes. The development of a reliable prediction system for this type of injury is crucial for reducing the incidence of cardiac complications in children receiving living donor liver transplantation (LDLT). However, establishing a practical myocardial injury prediction system for children with biliary atresia remains a considerable challenge.

AIM

To create and validate a nomogram model for predicting myocardial injury in children with biliary atresia who received LDLT.

METHODS

Clinical data from pediatric patients who received LDLT for biliary atresia between November, 2019 and January, 2022 were retrospectively analyzed. The complete dataset was randomly partitioned into a training set and a validation set at a ratio of 7:3. Least absolute shrinkage and selection operator regression was used to preliminarily screen out the predictors of myocardial injury. The prediction model was established *via* multivariable logistic regression and presented in the form of a nomogram.

RESULTS
This study included 321 patients, 150 (46.7%) of whom had myocardial injury. The participants were randomly allocated into two groups: A training group consisting of 225 patients and a validation group comprising 96 patients. The predictors in this nomogram included the preoperative neutrophil-to-lymphocyte ratio, high sensitivity C-reactive protein level, pediatric end-stage liver disease score and postreperfusion syndrome. The area under the curve for predicting myocardial injury was 0.865 in the training set and 0.856 in the validation set. The calibration curve revealed that the predicted values were very close to the actual values in the two sets. Decision curve analysis revealed that the prediction model offered a favorable net benefit.

CONCLUSION
The nomogram developed in this study effectively predicts myocardial injury in pediatric LDLT patients, showing good accuracy and potential for clinical application.

Key Words: Heart injuries; Nomograms; Child; Liver transplantation; Prognosis

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Core Tip: Myocardial injury is common during liver transplantation and is associated with a poor prognosis. Clinical data from pediatric patients who underwent living donor liver transplantation for biliary atresia were retrospectively analyzed. The prediction model was established *via* multivariable logistic regression and presented in the form of a nomogram. The predictors in this nomogram included the preoperative neutrophil-to-lymphocyte ratio, high sensitivity C-reactive protein level, pediatric end-stage liver disease score and postreperfusion syndrome. This nomogram effectively predicts myocardial injury during pediatric living donor liver transplantation, demonstrating strong discrimination, accuracy, and promising potential for clinical application.

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INTRODUCTION

Living donor liver transplantation (LDLT) is the main treatment for biliary atresia in children. Hepatic ischemia/reperfusion occurs after opening of the hepatic portal vein. In addition to causing liver damage, it also damages remote organs, including the heart, lungs, and kidneys[1-4]. This pathophysiological change poses enormous challenges to clinicians. A study from University of California, Los Angeles Medical Center revealed that 40.4% of adult liver transplant patients experienced myocardial injury during surgery, and their survival rate was lower than that of patients without such injury[1]. Previous research has also indicated that more than 40% of children receiving liver transplants experience perioperative myocardial damage, which leads to postoperative acute lung injury and a prolonged stay in the intensive care unit (ICU)[5]. Children with myocardial damage have extended stays in the ICU after surgery, experience delayed recovery of transplanted liver function, and have a significantly lower 1-year survival rate[6]. Therefore, establishing an effective myocardial injury prediction system, identifying high-risk patients, and formulating early myocardial injury prevention and control strategies are particularly important for reducing the incidence of cardiac complications in children and improving their prognosis.

Studies have shown that deep learning models pretrained on labeled 12-lead electrocardiogram can predict myocardial injury[7], but these models are ineffective in pediatric patients. Some plasma biomarkers, such as caspase-3, C-C motif chemokine ligand 2, vascular endothelial growth factor, copeptin, and miR-223, have clinical potential to predict myocardial damage early[8-10], but these markers are relatively new and usually cannot be detected by conventional analyzers, requiring specialized detection methods (such as enzyme linked immunosorbent assay or polymerase chain reaction), resulting in a lack of clinical implementation. At present, establishing a practical myocardial injury prediction system for children with biliary atresia remains a considerable challenge. The purpose of this study was to describe our clinical experience of LDLT in pediatric patients with biliary atresia, establish and verify a predictive nomogram model for myocardial injury, and provide a reference for the formulation of prevention and treatment strategies for myocardial injury associated with LDLT.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Institutional Review Committee at Tianjin First Central Hospital. Cases of pediatric patients (aged < 18 years) who underwent LDLT at this hospital between November 1, 2019 and January 1, 2022 were included in the present study. Children with a diagnosis other than biliary atresia, those with congenital heart disease, those who underwent liver retransplantation, and those with incomplete data were excluded.

Anesthesia and surgical procedures

All pediatric patients received midazolam, fentanyl, propofol, and rocuronium for general anesthesia induction. Anesthesia was maintained with propofol, remifentanil, fentanyl, cisatracurium, and sevoflurane. Mean arterial pressure, electrocardiogram, pulse oximetry, and central venous pressure were monitored during the operation. Ringer's acetate and albumin were administered as part of the fluid therapy regimen. Blood products or coagulation drugs were transfused according to the results of viscoelastic coagulation function monitoring. Acid-base and electrolyte balances were modulated on the basis of the blood gas values. The donors underwent left hepatectomy, and during transplantation, the transplanted liver was perfused with histidine-tryptophan-ketoglutarate solution. The recipients underwent piggyback liver transplantation without venous bypass and were admitted to the ICU for further treatment.

Clinical materials

We randomly divided the entire dataset at a ratio of 7:3 between the training cohort and the validation cohort. Baseline data, including age, sex, weight, height, the QTc interval, the left ventricular ejection fraction, high sensitivity C-reactive protein (hsCRP), hemoglobin, blood platelet counts, the platelet-to-lymphocyte ratio, aspartate aminotransferase (AST), alanine aminotransferase, albumin, total bilirubin (TB), creatinine, the neutrophil-to-lymphocyte ratio (NLR), the international normalized ratio, and the pediatric end-stage liver disease (PELD) score, were retrospectively extracted. All test results were obtained 3 days prior to transplantation. The donor-related parameters collected included graft cold ischemia time (CIT) and graft weight. The clinical parameters collected during the operation included vital signs, laboratory tests, anhepatic phase time, anesthesia time, surgical time, urine volume, blood loss, red blood cell transfusion volume, plasma transfusion volume and fluid infusion volume. The incidence of postreperfusion syndrome (PRS) was recorded. Using the above indicators as independent variables, factors that independently contribute to myocardial injury were screened through R language. The parameters for postoperative observation included the one-year survival rate; duration of ventilation; length of stay in the ICU; total hospital stay; peak TB, AST, and alanine aminotransferase levels during the initial week following LDLT; and the incidence of acute kidney injury.

Definition

In accordance with previous studies[5,6], myocardial injury in this study was defined as a cardiac troponin I (cTnI) level ≥ 0.07 ng/mL at the end of surgery. The definition of PRS was as follows: During the initial five minutes following liver graft reperfusion, the mean arterial pressure decreased by more than 30% in comparison to that at the end of the anhepatic phase, and this reduction persisted for a minimum duration of one minute[11]. The assessment of acute kidney injury was conducted in accordance with the criteria established by the guidelines[12].

Statistical analysis

Statistical analyses were performed using SPSS 27.0 and R software (version 4.3.2). A P value < 0.05 indicated statistical significance. The normality of continuous variables was evaluated using the Shapiro-Wilk test in conjunction with Q-Q plots. Normally distributed data are presented herein as mean ± SDs and were analyzed with t tests. Conversely, data that did not adhere to a normal distribution are presented as medians with interquartile ranges and were analyzed using Mann-Whitney U tests. Categorical variables are presented as counts and percentages and were analyzed using the Pearson χ^2 test. The area under the curve (AUC) was calculated *via* receiver operating characteristic (ROC) curve methodology. Least absolute shrinkage and selection operator regression was conducted with the "glmnet" package, multivariable logistic regression with "glm", and a nomogram was built using "rms". ROC curves were generated using "pROC", the Hosmer-Lemeshow test with "ResourceSelection", calibration curves with "rms", and decision curve analysis curves with "dcurves".

RESULTS

Patient screening and study design

During this study, 358 pediatric patients underwent LDLT. Fourteen individuals who were diagnosed with metabolic diseases, 2 individuals with Alagille syndrome, 2 individuals with Langerhans cell hyperplasia, 1 individual with a cavernous portal vein, 1 individual who needed liver retransplantation, 5 individuals with congenital heart disease, and 12 individuals whose data were incomplete were excluded. A cohort of 321 pediatric patients diagnosed with biliary atresia who underwent LDLT were included. Please refer to Figure 1 for the flow chart.

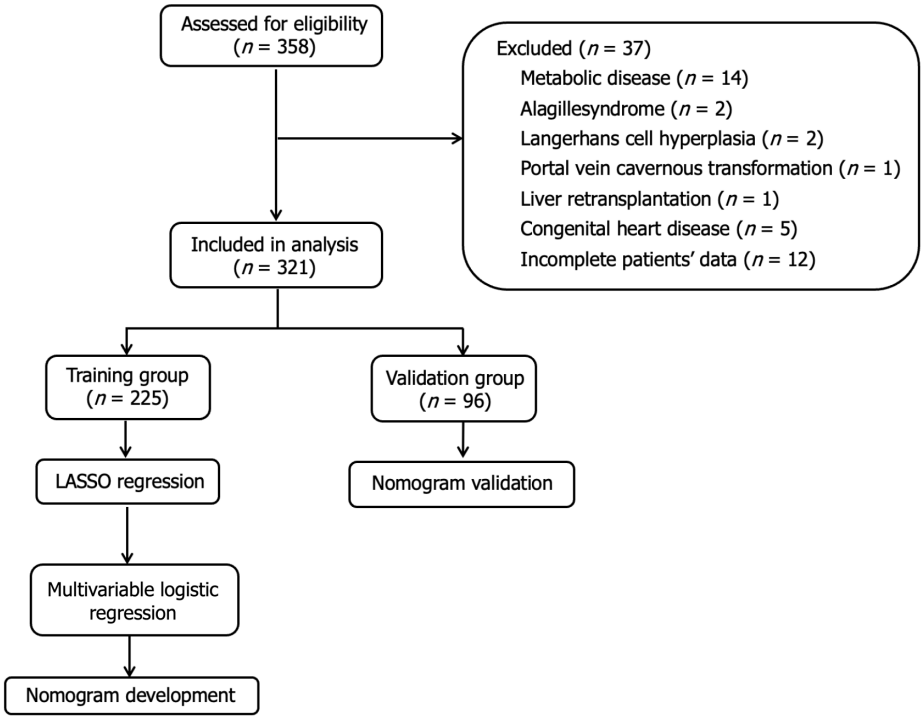


Figure 1 Flow chart of pediatric patients. LASSO: Least absolute shrinkage and selection operator.

Patient characteristics

As shown in Table 1, a total of 321 children who underwent LDLT were enrolled in the study, 150 (46.7%) of whom experienced intraoperative myocardial injury. The duration of postoperative stay in the ICU [3.0 (2.0-3.4) *vs* 2.0 (2.0-3.0) days, $P = 0.044$], peak TB [92 (66-123) *vs* 78 (50-115) μmol/L, $P = 0.004$], and AST [758 (506-1395) *vs* 666 (448-1180) U/L, $P = 0.027$] levels during the initial week following LDLT in the myocardial injury group were significantly greater than those in the nonmyocardial injury group. Patients in the myocardial injury group had a significantly lower 1-year survival rate than their counterparts in the nonmyocardial injury group did (92.0% *vs* 98.2%, $P = 0.017$). All enrolled patients were randomly divided into a training set ($n = 225$) and a validation set ($n = 96$) at a ratio of 7:3. There were no significant differences in the clinical variables between the training and validation sets (Table 2).

Predictors of myocardial injury

Taking the occurrence of myocardial injury as the dependent variable and the 39 selected indicators as independent variables, the optimal penalty coefficient was determined through 10-fold cross-verification, and its corresponding Lambda.1se value was 0.06345441. Four variables were selected: Preoperative NLR, hsCRP level, PELD score and PRS (as illustrated in Figure 2). The four variables identified through least absolute shrinkage and selection operator were incorporated into a multivariable logistic regression analysis. The results demonstrated that all four indicators functioned as independent risk factors linked to myocardial injury in children receiving liver transplantation ($P < 0.05$). The details are listed in Table 3.

Nomogram construction for myocardial injury during LDLT

As shown in Figure 3, a nomogram prediction model was established on the basis of the results of multivariable logistic regression analysis. The results of the predictive analysis revealed that the AUC for predicting the occurrence of myocardial injury in the training set was 0.865 (95% confidence interval: 0.819-0.912), the optimal cutoff value was 0.410, the specificity was 79.2%, the sensitivity was 80.0%, and the discriminatory ability was good (Figure 4A). The Hosmer-Lemeshow test ($\chi^2 = 10.006$, $P = 0.2646$) indicated a good fit for the training set. Bootstrap sampling with 1000 iterations confirmed strong alignment between the predicted and actual risks (Figure 5A).

Calibration verification of the nomogram

A total of 96 patients were included in the validation set, 45 (46.9%) of whom had myocardial injury. In the validation set, the AUC for predicting myocardial injury was 0.856, with a 95% confidence interval ranging from 0.783 to 0.928. This model demonstrated an optimal cutoff value of 0.585, a specificity of 94.1% and a sensitivity of 66.7%, as shown in Figure 4B. The Hosmer-Lemeshow test yielded $\chi^2 = 12.389$, $P = 0.1347$, indicating that the model fit was good. Internal calibration performed *via* 1000 bootstrap resamplings revealed that the predicted values were very close to the actual values (Figure 5B).

Table 1 Demographic characteristics and outcomes, *n* (%)

	Total (*n* = 321)	Non-myocardial injury (*n* = 171)	Myocardial injury (*n* = 150)	*P* value
Preoperative clinical data				
Age (month)	8.0 (6.0, 12.0)	9.0 (6.0, 16.5)	7.0 (6.0, 12.0)	0.002
Male gender	155 (48.3)	85 (49.7)	70 (46.7)	0.666
Weight (kg)	7.4 (6.5, 10.0)	7.9 (6.5, 11.0)	7.0 (6.5, 8.3)	0.003
Height (cm)	67 (63, 78)	70 (64, 82)	66 (63, 71)	0.002
QTc (ms)	405 (387, 423)	404 (387, 423)	406 (387, 430)	0.483
LVEF (%)	64 (62, 67)	64 (62, 66)	65 (62, 67)	0.254
NLR	0.78 (0.50, 1.29)	0.56 (0.42, 0.96)	1.10 (0.74, 1.88)	< 0.001
PLR	39.5 (28.2, 55.2)	38.4 (27.4, 51.0)	40.7 (28.9, 57.6)	0.067
hsCRP (mg/L)	5.31 (2.26, 12.78)	3.36 (0.92, 7.19)	9.66 (5.09, 26.43)	< 0.001
Albumin (g/L)	34.3 (32.0, 38.3)	35.0 (32.9, 39.5)	33.6 (31.0, 36.5)	0.001
TB (μmol/L)	225 (77, 317)	172 (39, 278)	258 (153, 352)	< 0.001
AST (U/L)	190 (119, 303)	191(113, 330)	186 (124, 290)	0.656
ALT (U/L)	113 (71, 174)	119 (65, 197)	110 (74, 153)	0.565
Creatinine (μmol/L)	13.0 (11.0, 16.0)	14.0 (12.0, 16.0)	12.0 (10.0, 15.0)	0.017
Hemoglobin (g/L), mean ± SD	93 ± 16	95 ± 17	90 ± 15	0.011
Platelet (10^9/L)	190 (127, 255)	190 (126, 235)	190 (130, 262)	0.378
INR	1.38 (1.13, 1.82)	1.25 (1.06, 1.66)	1.54 (1.32, 1.92)	< 0.001
PELD				< 0.001
< 14.5	103 (32.1)	82 (48.0)	21 (14.0)	
≥ 14.5	218 (67.9)	89 (52.0)	129 (86.0)	
Graft-related data				
Graft Weight (g)	244 (214, 280)	246 (214, 277)	244 (217, 280)	0.814
Graft CIT (minute)	86 (66, 112)	85 (66, 109)	86 (67, 115)	0.275
Intraoperative clinical data				
Laboratory test results before reperfusion				
pH, mean ± SD	7.388 ± 0.067	7.391 ± 0.068	7.384 ± 0.067	0.379
Base excess (mmol/L)	-4.40 (-6.40, -2.40)	-4.40 (-6.25, -1.90)	-4.40 (-6.65, -3.00)	0.338
Lactate (mmol/L)	2.60 (2.10, 3.40)	2.50 (1.90, 3.10)	2.70 (2.20, 3.70)	0.001
Hemoglobin (g/L)	82 (73, 92)	84 (75, 93)	81 (73, 91)	0.219
K (mmol/L)	3.70 (3.40, 4.10)	3.70 (3.50, 4.20)	3.70 (3.40, 4.07)	0.405
Ca (mmol/L)	1.09 (1.01, 1.16)	1.09 (1.01, 1.16)	1.08 (1.01, 1.16)	0.827
Vital signs before reperfusion				
Heart rate (beats/minute), mean ± SD	117 ± 13	119 ± 14	115 ± 12	0.029
MAP (mmHg)	58 (52, 66)	59 (54, 67)	56 (51, 64)	0.014
CVP (mmHg)	5 (3, 7)	5 (4, 7)	5 (3, 7)	0.821
Temperature (°C)	36.5 (35.9, 37.0)	36.5 (35.9, 37.0)	36.5 (35.8, 37.0)	0.528
Anhepatic phase time (minute)	48 (41, 58)	48 (40, 56)	49 (41, 62)	0.141
PRS				< 0.001

No	182 (56.7)	124 (72.5)	58 (38.7)	
Yes	139 (43.3)	47 (27.5)	92 (61.3)	
Data at the end of surgery				
Blood loss (mL)	300 (200, 400)	300 (200, 400)	300 (200, 400)	0.415
RBCs transfusion (units)	2.0 (2.0, 3.0)	2.0 (1.5, 3.0)	2.0 (2.0, 3.0)	0.069
FFP infusion (mL)	0 (0, 150)	0 (0, 100)	0 (0, 200)	0.005
Fluid infusion (mL)	1387 (1100, 1700)	1387 (1100, 1770)	1384 (1103, 1671)	0.784
Urine volume (mL)	400 (280, 600)	400 (300, 600)	400 (240, 600)	0.120
Surgical time (minute)	540 (490, 600)	540 (495, 600)	542 (481, 590)	0.730
Anaesthesia time (minute)	615 (560, 650)	615 (565, 650)	616 (555, 655)	0.650
Postoperative clinical data				
Ventilation time (minute)	205 (136, 340)	230 (147, 349)	185 (133, 320)	0.193
ICU stay (day)	2.5 (2.0, 3.0)	2.0 (2.0, 3.0)	3.0 (2.0, 3.4)	0.044
AKI				0.545
No	240 (74.8)	125 (73.1)	115 (76.7)	
Yes	81 (25.2)	46 (26.9)	35 (23.3)	
Liver function tests during the initial week following LDLT				
Peak TB (μmol/L)	84 (56, 117)	78 (50, 115)	92 (66, 123)	0.004
Peak AST (U/L)	697 (485, 1290)	666 (448, 1180)	758 (506, 1395)	0.027
Peak ALT (U/L)	586 (404, 1089)	585 (372, 1076)	592 (415, 1138)	0.247
Hospital stay (day)	21 (17, 27)	21 (17, 30)	21 (17, 25)	0.158
1-year survival rate	306 (95.3)	168 (98.2)	138 (92.0)	0.017

LVEF: Left ventricular ejection fraction; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; hsCRP: High sensitivity C-reactive protein; TB: Total bilirubin; AST: Aspartate transaminase; ALT: Alanine transaminase; INR: International normalized ratio; PELD: Pediatric end-stage liver disease; CIT: Cold ischemia time; MAP: Mean arterial pressure; CVP: Central venous pressure; PRS: Postreperfusion syndrome; RBC: Red blood cell; FFP: Fresh frozen plasma; ICU: Intensive care unit; AKI: Acute kidney injury; LDLT: Living donor liver transplantation.

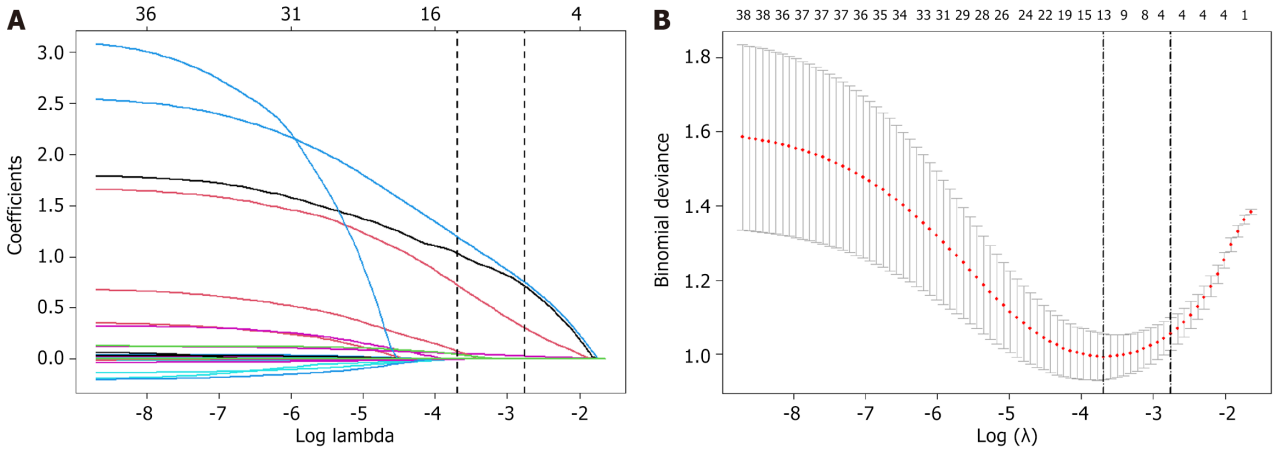


Figure 2 Least absolute shrinkage and selection operator regression. A: Coefficient curve of independent variables; B: Selection of the best independent variables by least absolute shrinkage and selection operator regression and 10-fold cross validation.

Analysis of the clinical practicality of the prediction model

In the decision curve analysis, the green horizontal lines signify the scenario of no intervention, where the net benefit is zero, whereas the red lines represent the intervention applied to all patients (Figure 6). The predictive model demonstrated a substantial net benefit, with a broad high-risk threshold probability range observed in both the training and validation groups, highlighting its clinical usefulness.

Table 2 Clinical data of patients in the training and validation sets, *n* (%)

	Training set (*n* = 225)	Validation set (*n* = 96)	*P* value
Preoperative clinical data			
Age (month)	8.0 (6.0, 12.0)	9.0 (6.0, 16.3)	0.434
Male gender	108 (48.0)	47 (49.0)	0.972
Weight (kg)	7.3 (6.5, 9.5)	7.5 (6.5, 10.0)	0.742
Height (cm)	67 (64, 76)	67 (63, 79)	0.621
QTc (ms)	405 (387, 423)	407 (387, 422)	0.862
LVEF (%)	64 (62, 67)	65 (62, 67)	0.693
NLR	0.79 (0.51, 1.28)	0.78 (0.49, 1.43)	0.878
PLR	39.5 (27.5, 55.0)	42.5 (30.3, 55.2)	0.111
hsCRP (mg/L)	5.31 (2.53, 13.93)	5.04 (1.95, 10.63)	0.262
Albumin (g/L)	34.5 (32.0, 38.3)	34.3 (31.7, 38.3)	0.338
TB (μmol/L)	226 (78, 317)	223 (65, 314)	0.372
AST (U/L)	190 (123, 306)	191 (108, 294)	0.488
ALT (U/L)	115 (68, 179)	107 (72, 154)	0.680
Creatinine (μmol/L)	13.0 (11.0, 16.0)	13.0 (11.0, 15.0)	0.933
Hemoglobin (g/L), mean ± SD	93 ± 16	93 ± 17	0.916
Platelet (10^9/L)	190 (128, 250)	184 (118, 265)	0.451
INR	1.40 (1.13, 1.82)	1.38 (1.13, 1.83)	0.953
PELD score			0.937
< 14.5	73 (32.4)	30 (31.3)	
≥ 14.5	152 (67.6)	66 (68.8)	
Graft-related data			
Graft weight (g)	244 (218, 277)	246 (212, 281)	0.849
Graft CIT (minute)	85 (66, 112)	88 (68, 119)	0.556
Intraoperative clinical data			
Laboratory test results before reperfusion			
pH, mean ± SD	7.39 ± 0.07	7.38 ± 0.07	0.223
Base excess (mmol/L)	-4.40 (-6.20, -2.20)	-4.40 (-6.82, -2.85)	0.630
Lactate (mmol/L)	2.60 (2.00, 3.40)	2.70 (2.20, 3.40)	0.503
Hemoglobin (g/L)	84 (74, 92)	81 (73, 92)	0.572
K (mmol/L)	3.80 (3.50, 4.10)	3.65 (3.40, 4.03)	0.139
Ca (mmol/L)	1.09 (1.01, 1.17)	1.08 (1.01, 1.14)	0.306
Vital signs before reperfusion			
Heart rate (beats/minute), mean ± SD	116 ± 13	118 ± 12	0.202
MAP (mmHg)	59 (52, 66)	58 (53, 64)	0.736
CVP (mmHg)	5 (3, 7)	5 (3, 7)	0.539
Temperature (°C)	36.5 (35.9, 37.0)	36.5 (36.0, 37.1)	0.570
Anhepatic phase duration (minute)	49 (41, 59)	46 (40, 55)	0.063
PRS			0.611
No	125 (55.6)	57 (59.4)	
Yes	100 (44.4)	39 (40.6)	

Data at the end of surgery			
Blood loss (mL)	300 (230, 400)	300 (200, 400)	0.079
RBCs transfusion (units)	2.0 (2.0, 3.0)	2.0 (2.0, 2.5)	0.117
FFP infusion (mL)	0 (0, 150)	0 (0, 135)	0.650
Fluid infusion (mL)	1400 (1109, 1745)	1334 (1100, 1652)	0.403
Urine volume (mL)	400 (260, 600)	425 (300, 600)	0.628
Surgical time (minute)	540 (480, 596)	550 (504, 601)	0.070
Anaesthesia time (minute)	615 (555, 649)	625 (579, 663)	0.066
Myocardial injury	105 (46.7)	45 (46.9)	0.973
Postoperative clinical data			
Ventilation time (minute)	205 (135, 320)	208 (139, 350)	0.729
ICU stay (day)	2.0 (2.0, 3.0)	3.0 (2.0, 3.1)	0.101
AKI			0.839
No	167 (74.2)	73 (76.0)	
Yes	58 (25.8)	23 (24.0)	
Liver function tests during the initial week following LDLT			
Peak TB (μmol/L)	83 (56, 121)	86 (56, 111)	0.700
Peak AST (U/L)	699 (483, 1333)	691 (497, 1220)	0.762
Peak ALT (U/L)	588 (408, 1084)	579 (385, 1096)	0.603
Hospital stay (day)	21 (17, 26)	21 (16, 29)	0.609
One-year survival rate	215 (95.6)	91 (94.8)	0.776

LVEF: Left ventricular ejection fraction; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; hsCRP: High sensitivity C-reactive protein; TB: Total bilirubin; AST: Aspartate transaminase; ALT: Alanine transaminase; INR: International normalized ratio; PELD: Pediatric end-stage liver disease; CIT: Cold ischemia time; MAP: Mean arterial pressure; CVP: Central venous pressure; PRS: Postreperfusion syndrome; RBC: Red blood cell; FFP: Fresh frozen plasma; ICU: Intensive care unit; AKI: Acute kidney injury; LDLT: Living donor liver transplantation.

Table 3 Multivariable logistic regression analysis of risk factors for myocardial injury

Risk factors	OR	95%CI	*P* value
PELD ≥ 14.5	4.441	2.066-10.120	< 0.001
hsCRP	1.085	1.045-1.133	< 0.001
NLR	3.380	1.766-7.282	0.001
PRS	4.662	2.330-9.676	< 0.001

OR: Odds ratio; CI: Confidence interval; PELD: Pediatric end-stage liver disease; hsCRP: High sensitivity C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PRS: Postreperfusion syndrome.

DISCUSSION

CTnI is an important marker for the early diagnosis of myocardial injury[13,14]. When cardiomyocytes are damaged, their concentration in the blood increases, indicating myocardial injury. In the pediatric population, troponins are strongly correlated with the extent of myocardial damage and can be used as predictors of subsequent cardiac recovery and mortality[15]. From Dou *et al*'s study[16], we can observe the change trend of cTnI levels in children during LDLT: It increases during the operation, increases 8-12 times at the end of the operation, reaches the peak value, and returns to the pretransplantation level 3 days after the operation. In accordance with Sheng *et al*'s study[5] and the instrument manufacturer's instructions, a cTnI concentration ≥ 0.07 ng/mL indicated myocardial injury. The study revealed that 150 patients (46.7%) experienced myocardial injury during surgery, and the independent risk factors for this injury included a high NLR, high hsCRP level, high PELD score and the occurrence of PRS. Many factors, such as severe preoperative conditions, severe fluctuations in circulation during surgery and inflammatory reactions in the body, may lead to

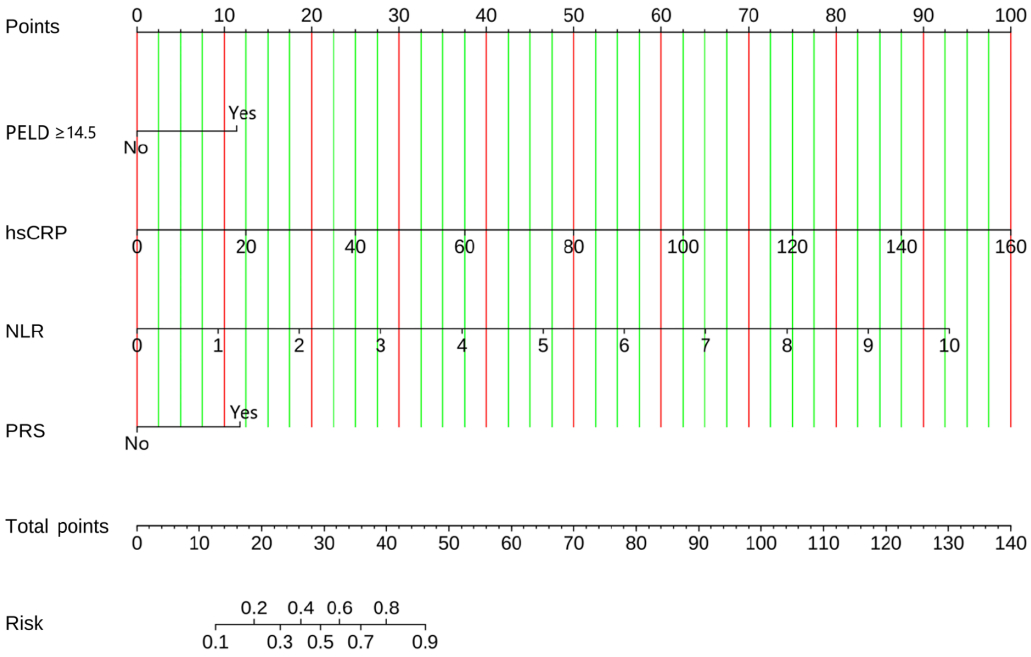


Figure 3 A nomogram to predict myocardial injury during living donor liver transplantation. PELD: Pediatric end-stage liver disease; hsCRP: High sensitivity C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PRS: Postreperfusion syndrome.

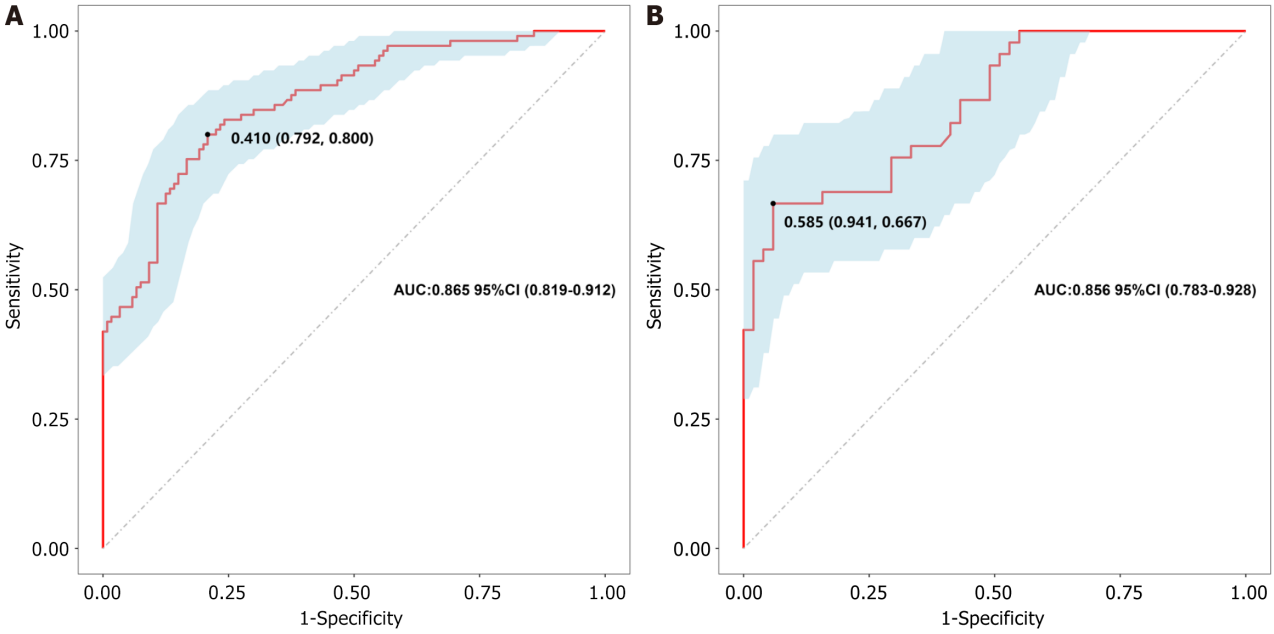


Figure 4 Receiver operating characteristic curves for predicting myocardial injury in pediatric patients in the training and validation sets. A: Receiver operating characteristic curves for predicting myocardial injury in pediatric patients in the training set; B: Receiver operating characteristic curves for predicting myocardial injury in pediatric patients in the validation set. AUC: Area under the curve; CI: Confidence interval.

myocardial injury.

The NLR, which is the ratio of the neutrophil count to the lymphocyte count in peripheral blood, is a readily available laboratory indicator and a marker of systemic inflammation[17]. Cirrhosis and portal hypertension are often accompanied by bacterial translocation and endotoxemia, which can induce an increase in blood neutrophil counts and a decrease in total lymphocyte counts, as well as elevated levels of systemic proinflammatory cytokines, which can lead to cardiac dysfunction[18,19]. Studies have shown that the main cause of liver transplantation-related myocardial injury is the inflammatory response[20,21]. Bezinover *et al*[22] demonstrated that the massive release of tumor necrosis factor alpha in the early stage of reperfusion of the new liver could lead to hemodynamic instability and a heightened requirement for norepinephrine. Marfella *et al*[23] reported that tumor necrosis factor alpha could induce the overexpression of nitric oxide synthase in myocardial cells, leading to massive production of nitric oxide, reducing the response of myofilaments to Ca^{2+}, and thus exerting a negative inotropic effect on the myocardium. A study by Nylec *et al*[24] revealed that the NLR

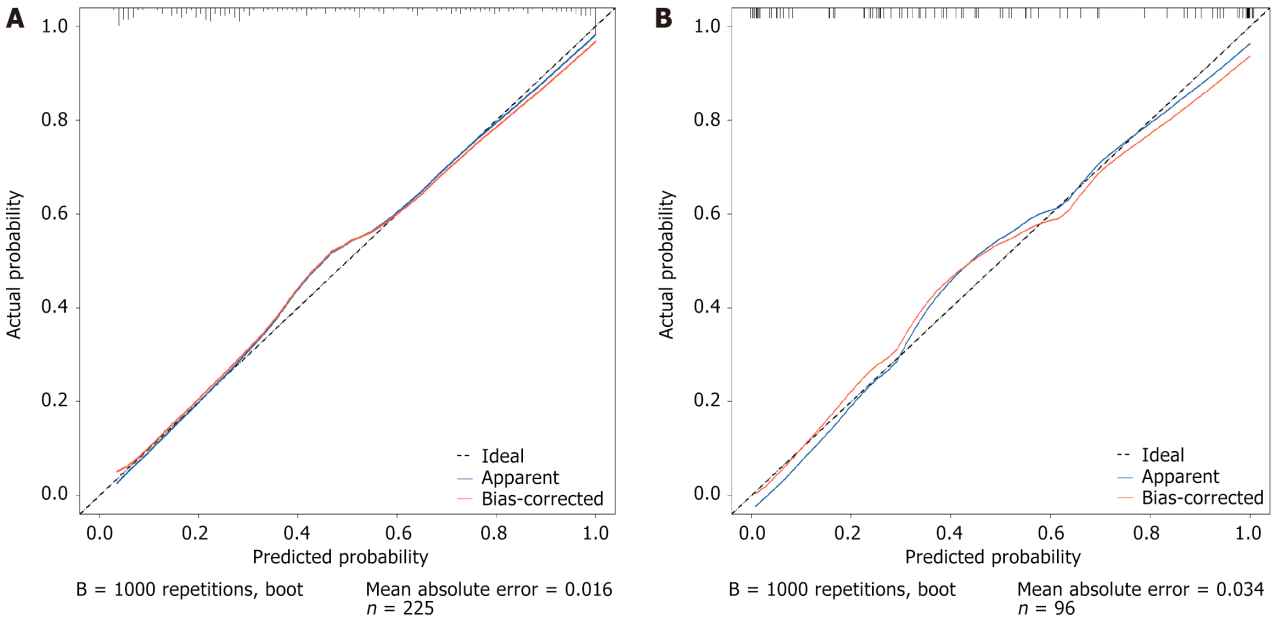


Figure 5 Calibration curves for the training and validation sets. A: Calibration curves for the training set; B: Calibration curves for the validation set.

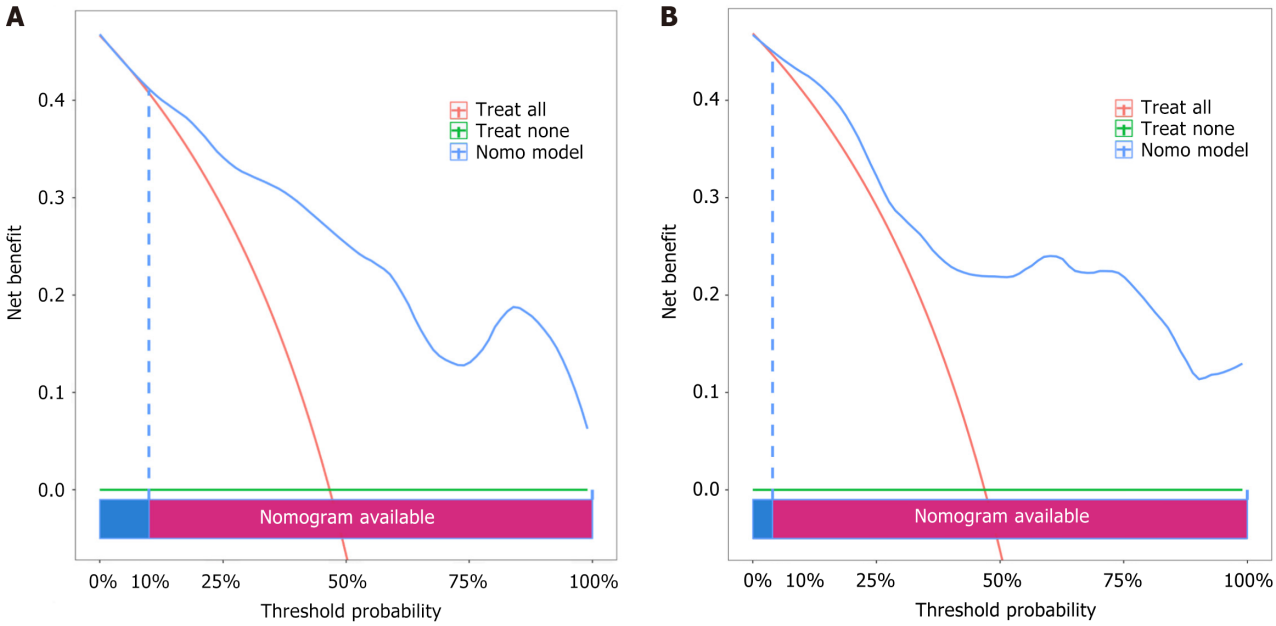


Figure 6 Clinical decision curve analysis for the training and validation sets. A: Clinical decision curve analysis for the training set; B: Clinical decision curve analysis for the validation set.

is a risk factor for increased graft loss and mortality in adult orthotopic liver transplant patients. The increase in the NLR before surgery in patients with cirrhosis may indicate endotoxemia and an excessive inflammatory response in the body, which is related not only to myocardial damage but also to a poor prognosis.

CRP serves as a highly sensitive biomarker for systemic inflammation and is a good indicator of the severity of myocardial damage[25]. CRP plays a proinflammatory role by activating the complement system and stimulating natural killer cells[26]. In rat liver ischemia/reperfusion studies, CRP was found to have activated C3 in hepatocytes, indicating that it is a key mediator of classical complement activation[27]. Higher hsCRP levels are closely associated with lower systolic blood pressure and the development of cardiac complications[28]. Elevated hsCRP levels before liver transplantation are associated with increased cardiovascular events after liver transplantation[29].

The PELD score serves as a vital tool for assessing the severity and future outlook of end-stage liver disease in children [30]. A retrospective analysis conducted by Sheng *et al*[31] involving 112 children with biliary atresia who underwent LDLT revealed that the preoperative PELD score was positively correlated with the intraoperative increase in cardiac troponin I levels. Specifically, higher PELD scores were associated with increased serum cardiac troponin I concentrations during surgery. Oh *et al*[32] reported that a PELD score greater than 25 independently predicts graft function loss after

pediatric LDLT. Pan *et al*'s study revealed that the PELD score was an independent predictor of 1-year and 3-year survival[33]. Patients with high PELD scores are more likely to suffer from intraoperative myocardial injury and therefore have a poor prognosis.

Living-donor liver transplantation is the main treatment for biliary atresia in children. The transition from the anhepatic stage to the neohepatic stage is the most critical period of surgery. During this phase, abrupt and significant hemodynamic alterations may occur, resulting in decreased myocardial contractility, sustained hypotension, bradycardia, or severe arrhythmias. These adverse events are typical features of PRS[34-36]. PRS is recognized as one of the most prevalent complications associated with liver transplantation, with an incidence rate ranging from approximately 12% to 55%[36-38]. This syndrome may result in a slower healing process for transplanted liver functions, longer hospital stays, and an increased risk of mortality, thereby significantly impacting the postoperative quality of life of pediatric patients [36,38]. PRS can be caused by multiple factors, such as metabolic acidosis, hyperkalemia, hypocalcemia, hypothermia, inflammatory mediators, increased CIT and increased severity of liver disease[11,39-42]. PRS prevention and treatment strategies should be actively adopted to reduce the risk of myocardial injury. It is essential to improve the patient's overall condition before surgery by implementing measures such as infection control, nutritional support, and the correction of anemia and hypoproteinemia. During the operation, we should optimize the patient's blood volume status, take active temperature protection measures, administer anti-inflammatory medications, correct acid-base imbalances and electrolyte disturbances, shorten the CIT as much as possible, and apply pressors before reperfusion. The above measures may be practical strategies for managing PRS.

There is no related research on the establishment of a predictive nomogram model for myocardial injury in pediatric liver transplantation through a large-sample retrospective study, so this preliminary exploratory study is valuable. Compared with the conventional logistic regression model, the nomogram model offers greater simplicity, enhanced intuitiveness, and increased practical utility in clinical settings. Importantly, this study had a small sample size, lacked external validation, and excluded some patients because of incomplete data, potentially causing selection bias and limitations. In addition, anesthesia management varies across centers, which may bias the results of single-center studies. Therefore, future analyses should be further verified using multicenter large sample data. While the current model provides a robust prediction of myocardial injury on the basis of a set of preoperative and intraoperative variables, there are numerous opportunities to refine and expand its predictive power by incorporating additional predictors. Future studies can explore the role of advanced biomarkers, imaging findings, and other novel technologies that could further increase the model's accuracy and clinical utility.

CONCLUSION

The nomogram developed in this study effectively predicts myocardial injury in pediatric LDLT, showing good accuracy and potential for clinical application.

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FOOTNOTES

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Informed consent statement: Since this was a retrospective study with the inability to access to the patients, the Ethics Committee granted a waiver for the requirement of informed consent.

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ORIGINAL ARTICLE

Retrospective Study

Perioperative risk factors for prognosis in patients undergoing radical esophagectomy: A retrospective study

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Abstract

BACKGROUND

Esophageal cancer constitutes one of the most aggressive malignant neoplasms associated with poor clinical outcomes. While surgical resection remains the cornerstone of curative intervention, optimization of perioperative care protocols has emerged as an essential strategy to reduce postoperative complications and potentially improve long-term survival rates in patients undergoing esophagectomy. However, substantial debate persists regarding the relative importance of various perioperative risk factors and their impact on post-resection outcomes.

AIM

To identify perioperative factors affecting prognosis after radical esophagectomy, aiming to improve patient outcomes through targeted interventions.

METHODS

A retrospective study analyzed 378 patients with esophageal cancer who underwent radical esophagectomy (McKeown, Sweet, or Ivor-Lewis procedures) from January 2022 through December 2023. All operations were performed by experienced surgeons following standardized perioperative protocols. The investigation gathered data on patient demographics, surgical parameters, tumor pathology (using the 8th edition American Joint Committee on Cancer staging system), and survival outcomes. Statistical analyses utilized Kaplan-Meier estimates and Cox proportional hazards modeling, with adjustment for confounding

variables.

RESULTS

Multivariate Cox proportional hazards analysis identified three independent predictors of survival: Tumor-node-metastasis staging [Hazard ratio (HR) = 2.31, 95% confidence interval (CI): 1.72-3.10, $P < 0.001$], tumor differentiation (moderate: HR = 1.46, 95%CI: 1.02-2.09, $P = 0.038$; poor: HR = 2.15, 95%CI: 1.47-3.14, $P < 0.001$), and extended postoperative analgesic use (> 5 days) (HR = 1.43, 95%CI: 1.08-1.89, $P = 0.012$). Kaplan-Meier analysis demonstrated significantly lower overall survival rates in patients requiring analgesics for > 5 days compared to ≤ 5 days ($P = 0.003$), with consistent patterns observed for both opioid ($P = 0.019$) and nonsteroidal anti-inflammatory drug use ($P = 0.028$). The extended analgesic group exhibited a higher proportion of elderly patients (48.47% *vs* 35.57%, $P = 0.015$), while other baseline characteristics and tumor features remained comparable between groups.

CONCLUSION

Tumor-node-metastasis staging, tumor differentiation, and duration of postoperative analgesic use independently predict survival following radical esophagectomy, underscoring the significance of optimal pain management protocols.

Key Words: Radical esophagectomy; Perioperative management; Prognostic factors; Postoperative analgesic use; Survival analysis

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Core Tip: In this retrospective analysis of 378 patients who underwent radical esophagectomy for esophageal cancer, we identified tumor-node-metastasis staging, tumor differentiation, and extended postoperative analgesic use (> 5 days) as independent predictors of overall survival. Of particular significance was the adverse impact of prolonged administration of both opioids and nonsteroidal anti-inflammatory drugs on survival outcomes. These findings emphasize the critical importance of precise perioperative management, specifically regarding optimal pain control protocols, in enhancing patient outcomes. Further validation through multicenter, prospective studies and investigation of underlying mechanisms is warranted to optimize perioperative care strategies and improve long-term survival rates in this patient population.

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INTRODUCTION

Esophageal cancer is a malignant neoplasm originating from esophageal epithelial cells that can develop in any segment of the esophagus, with squamous cell carcinoma being the predominant histologic type. While early-stage disease may be asymptomatic, advanced cases typically manifest with dysphagia and food obstruction[1]. Global cancer statistics from 2020 indicate that esophageal cancer ranks seventh among all malignancies worldwide, with China accounting for over half of incident cases[2]. In China, as of 2016, esophageal cancer ranked sixth in incidence and fifth in mortality among all malignancies, constituting a substantial public health burden[3]. The disease is characterized by high malignant potential and poor outcomes, with advanced-stage patients in China exhibiting only a 26% five-year survival rate[4].

Currently, surgical intervention remains the most definitive curative approach for esophageal cancer[5]. Improved surgical mortality rates can be attributed to advances in operative techniques, standardized perioperative protocols, and widespread implementation of multidisciplinary treatment strategies. However, radical esophagectomy remains a highly invasive procedure characterized by prolonged operative duration, challenging surgical exposure, and complex anatomical relationships. The high incidence of postoperative complications, often exacerbated by concurrent comorbidities, significantly impacts prognosis and quality of life[6].

Perioperative management is fundamental to esophageal cancer treatment, with surgical outcomes and patient prognosis directly linked to the quality of perioperative care[7]. Despite technological and therapeutic advances, esophageal cancer surgery continues to carry substantial morbidity and mortality risks. Key perioperative challenges include inadequate pain control, respiratory complications, delayed gastrointestinal recovery, and poor nutritional status [8,9]. Pain management is particularly crucial, as insufficient analgesia can precipitate respiratory compromise, impair early mobilization, and amplify stress response, potentially compromising both immediate recovery and long-term outcomes.

While numerous studies have investigated perioperative risk factors[10-12], including age, nutritional status, comorbidities, surgical approach, operative duration, blood loss, and extent of lymphadenectomy, their prognostic significance remains controversial with inconsistent findings across studies. The emergence of enhanced recovery after surgery

protocols has transformed perioperative management strategies[13], with optimal pain control as a cornerstone component. Although optimized perioperative care can reduce surgical complications and potentially enhance long-term survival, implementing comprehensive care protocols presents practical challenges due to patient heterogeneity, varying pain thresholds, and resource limitations.

Our study aims to comprehensively evaluate perioperative factors influencing outcomes following radical esophagectomy. Through retrospective analysis of institutional clinical data, we seek to identify key perioperative risk factors associated with adverse postoperative outcomes and decreased survival, assess their relative prognostic impact, determine potentially modifiable factors amenable to intervention, and establish evidence-based recommendations for perioperative management. These findings will guide clinical decision-making and ultimately enhance treatment outcomes and quality of life for patients with esophageal cancer.

MATERIALS AND METHODS

Study design and patients

This retrospective study analyzed clinical data from 378 patients who underwent radical esophagectomy for esophageal cancer at the Department of Thoracic Surgery, Fourth Hospital of Hebei Medical University between January 2022 and December 2023. Patients were eligible for inclusion if they met the following criteria: (1) Histologically confirmed esophageal cancer by preoperative endoscopic biopsy; (2) Absence of distant metastasis on preoperative imaging studies, including contrast-enhanced chest and abdominal computed tomography, cervical ultrasonography, and whole-body positron emission tomography-computed tomography; (3) Medical fitness for surgery with no contraindications; (4) Completion of standard radical esophagectomy; and (5) Availability of complete clinical records. Exclusion criteria comprised: (1) Prior neoadjuvant therapy; (2) History of other malignancies; (3) Presence of severe cardiac, pulmonary, hepatic, or renal dysfunction; (4) Intraoperative discovery of distant metastases precluding complete resection; (5) Perioperative mortality; and (6) Loss to follow-up or incomplete follow-up data.

Surgical methods

All procedures were performed by experienced surgeons (associate chief physician or above) with a minimum of 15 years of expertise in esophageal cancer surgery. The surgical approach (McKeown three-incision, Sweet left thoracic, or Ivor-Lewis two-incision) was selected based on tumor location, patient characteristics, and surgical expertise. All operations adhered to standard oncological principles of radical esophagectomy, ensuring complete resection of the diseased esophageal segment and regional lymph nodes with negative margins.

The surgical procedure was performed under general anesthesia with double-lumen endotracheal intubation. Patient positioning varied by approach: Supine with contralateral head rotation for cervical access, lateral decubitus with 30° elevation for thoracic access, and supine for abdominal access. The thoracic phase involved esophageal mobilization and systematic lymphadenectomy of the periesophageal, subcarinal, paratracheal, and supradiaphragmatic nodes. The abdominal phase included gastric mobilization along greater and lesser curvatures while preserving the right gastroepiploic artery, accompanied by lymph node dissection around the cardia, left gastric artery, and celiac axis.

Gastrointestinal continuity was restored using a 3-4 cm wide gastric tube, created with a linear stapler along the greater curvature. The gastric conduit was routed through either the posterior mediastinum or retrosternal space for esophagogastric anastomosis, performed either mechanically or manually, based on anatomical considerations and surgeon preference. Standard placement of thoracic drainage and nasogastric tubes was performed. Strict adherence to oncological principles included "no-touch" technique to minimize tumor manipulation. All specimens underwent pathological examination for margin status and lymph node involvement.

Perioperative management

Preoperative preparation: All patients underwent comprehensive preoperative evaluation upon admission. Standard assessment included complete blood count, liver and kidney function tests, coagulation profile, and cardiopulmonary function evaluation. The American Society of Anesthesiologists (ASA) classification was applied to patients aged 65 years or older or those with comorbidities. Nutritional status was evaluated using the Nutritional Risk Screening 2002 scoring system; patients scoring ≥ 3 or with serum albumin < 35 g/L received nutritional supplementation. Anemia (hemoglobin < 120 g/L in men, < 110 g/L in women) was corrected preoperatively. Pulmonary function was assessed through detailed history, physical examination, spirometry, and arterial blood gas analysis. Patients with impaired pulmonary function received respiratory physiotherapy and nebulization treatment. Medical conditions including hypertension and diabetes were optimized to achieve target parameters. Bowel preparation was conducted one day preoperatively using oral polyethylene glycol electrolyte solution or mannitol, with 8-hour fasting and 4-hour clear liquid restrictions prior to surgery. Intravenous access was established 24 hours preoperatively, and prophylactic second-generation cephalosporins were administered 30 minutes before incision. All patients received psychological support and detailed operative instructions.

Anesthesia method: Combined general and thoracic epidural anesthesia was utilized. Standard monitoring included electrocardiogram, blood pressure, and pulse oximetry, complemented by invasive arterial pressure monitoring. Anesthesia induction was performed with midazolam (0.05 mg/kg), sufentanil (0.5 μg/kg), propofol (1.5-2.0 mg/kg), and cisatracurium (0.2 mg/kg). A double-lumen endobronchial tube was positioned using fiberoptic bronchoscopic guidance. Anesthesia maintenance was achieved through continuous propofol (4-12 mg/kg/h) and remifentanil (0.1-0.3 μg/kg/

minute) infusion, with intermittent cisatracurium administration. Volume-controlled ventilation was sustained with 6-8 mL/kg tidal volume, 12-14 respirations/min, and end-tidal CO_2 maintained at 35-45 mmHg. Single-lung ventilation parameters were modified accordingly, with positive end-expiratory pressure applied as needed. Mean arterial pressure was maintained at or above 65 mmHg using vasoactive medications when required. Temperature, urine output, and blood gas values were monitored to preserve physiological homeostasis.

Postoperative management: Patients were transferred to the intensive care unit for immediate postoperative monitoring. Analgesia was administered through a patient-controlled analgesia pump (sufentanil + tropisetron) in conjunction with thoracic epidural analgesia. Continuous monitoring included vital parameters, drainage characteristics, and urinary output. Early mobilization, pulmonary exercises, and nebulization therapy were implemented to prevent respiratory complications. Endotracheal suctioning was performed at 2-4 hours intervals. Nutritional support followed a systematic approach: Enteral nutrition *via* nasogastric tube was initiated 24 hours postoperatively, supplemented with parenteral nutrition. Oral intake commenced between postoperative days 3-5 following verification of anastomotic integrity, progressing from clear liquids to soft diet. Prophylactic antibiotic therapy was typically discontinued within 48-72 hours. Deep venous thrombosis prophylaxis included early ambulation, intermittent pneumatic compression, and subcutaneous low-molecular-weight heparin administration. Thoracic drainage tubes were removed when output was < 200 mL/day and serous. Patients were transferred to the general ward upon clinical stabilization, with immediate intervention for any complications.

Data collection

Baseline characteristics collected included demographic variables (age, sex, body mass index), medical history (hypertension, diabetes mellitus, chronic gastritis), lifestyle factors (smoking status, alcohol consumption), and clinical parameters [ASA classification, New York Heart Association (NYHA) functional classification, preoperative glomerular filtration rate]. The ASA physical status classification system was defined as follows: (1) Class I: Normal healthy patient; (2) Class II: Patient with mild systemic disease; (3) Class III: Patient with severe systemic disease limiting activity; (4) Class IV: Patient with severe systemic disease that poses constant threat to life; (5) Class V: Moribund patient not expected to survive without surgery; and (6) The NYHA functional classification was categorized as: Class I: No limitation of physical activity; class II: Mild limitation with symptoms during ordinary activity; class III: Marked limitation with symptoms during less than ordinary activity; and class IV: Symptoms at rest with any physical activity causing discomfort.

Operative data included anesthetic technique, surgical approach, anastomotic location, operative duration, length of postoperative analgesia, adjuvant therapy (chemotherapy or radiotherapy), and postoperative complications (pneumonia, pleural effusion). Tumor characteristics were evaluated according to the 8th edition of the American Joint Committee on Cancer staging system, including tumor-node-metastasis (TNM) stage, tumor location and maximum diameter, histologic grade, depth of invasion, perineural invasion, lymphovascular invasion, and lymph node status.

TNM Staging was classified as: Stage 0: Carcinoma in situ; stage I: Local tumor invasion without nodal involvement; stage II: (1) Muscular invasion without nodal involvement; and (2) With regional lymph node metastasis; stage III: Advanced local invasion with regional lymph node involvement; and stage IV: Distant metastasis. The primary endpoint was all-cause mortality, defined as death from any cause during the follow-up period. Mortality was determined through active follow-up with participants or their next of kin. Date and cause of death were documented. Participants were followed from the index date until death, loss to follow-up, or study completion, whichever occurred first.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 26.0, IBM Corporation, Armonk, NY, United States). The normality of continuous variables' distribution was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean ± SD and compared using independent-samples *t*-tests, while non-normally distributed variables were presented as median (interquartile range) and analyzed using the Mann-Whitney *U* test. Variance homogeneity was evaluated using Levene's test. Categorical variables were expressed as frequencies (percentages) and analyzed using Pearson's χ^2 test or Fisher's exact test when expected cell counts were less than 5.

Overall survival was calculated using the Kaplan-Meier method, with intergroup differences assessed using the log-rank test. The proportional hazards assumption for Cox regression analysis was verified through examination of Schoenfeld residuals. Prognostic factors were identified through univariate and multivariate Cox proportional hazards models. To control for potential confounding factors, the following variables were selected a priori based on clinical significance and published literature: Age, sex, body mass index, ASA physical status classification, comorbidities, tumor stage, surgical approach, and operative time. Variables showing $P \leq 0.1$ in univariate analysis were included in the multivariate Cox regression model. The magnitude and precision of associations were quantified using hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). All statistical tests were two-sided, with statistical significance defined as $P < 0.05$.

RESULTS

Univariate analysis of perioperative Cox proportional hazards model for overall survival

Baseline characteristics: Advanced age (≥ 65 years; HR = 1.52, 95%CI: 1.18-1.96, $P = 0.001$), ASA physical status class IV

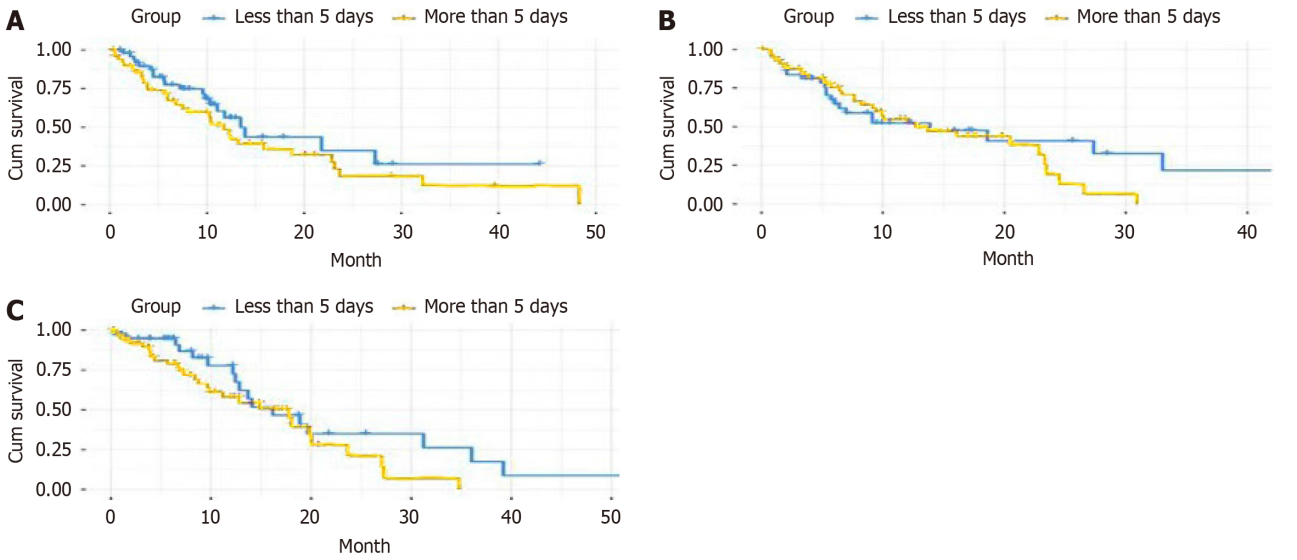


Figure 1 Duration of analgesic use after esophageal cancer surgery. A: Kaplan-Meier analysis of different analgesic use duration after radical esophagectomy; B: Kaplan-Meier analysis of different opioid analgesics use duration after radical esophagectomy; C: Kaplan-Meier Analysis of different nonsteroidal anti-inflammatory drug analgesics use duration after radical esophagectomy.

(HR = 1.45, 95%CI: 1.08-1.95, P = 0.01), and NYHA functional class III (HR = 1.68, 95%CI: 1.12-2.52, P = 0.01) demonstrated significant associations with decreased overall survival. Hypertension and diabetes exhibited borderline significance (P < 0.10) (Table 1).

Surgery-related factors: Extended postoperative analgesic administration (> 5 days; HR = 1.62, 95%CI: 1.24-2.12, P < 0.001), postoperative pneumonia (HR = 1.58, 95%CI: 1.21-2.06, P = 0.001), pleural effusion (HR = 1.42, 95%CI: 1.07-1.88, P = 0.02), and adjuvant chemoradiotherapy (HR = 1.45, 95%CI: 1.12-1.88, P = 0.01) were associated with inferior survival outcomes. Prolonged operative time showed marginal correlation with adverse outcomes (HR = 1.00, P = 0.05) (Table 2).

Tumor pathological characteristics: Advanced TNM stage (III/IV; HR = 2.85, 95%CI: 2.15-3.78, P < 0.001), increased tumor size (≥ 3 cm; HR = 1.68, 95%CI: 1.29-2.19, P < 0.001), submucosal invasion (HR = 1.92, 95%CI: 1.46-2.52, P < 0.001), poor differentiation (HR = 2.42, 95%CI: 1.67-3.51, P < 0.001), perineural invasion (HR = 1.75, 95%CI: 1.33-2.30, P < 0.001), vascular invasion (HR = 1.89, 95%CI: 1.42-2.52, P < 0.001), and lymph node metastasis (HR = 2.32, 95%CI: 1.77-3.04, P < 0.001) demonstrated significant correlation with decreased survival (Table 3).

Comparison between extended (> 5 days) and short-term (≤ 5 days) analgesic administration

The extended analgesic group demonstrated a higher proportion of elderly patients (≥ 65 years; 48.47% *vs* 35.57%, P = 0.015) (Table 4). Other baseline characteristics, surgery-related parameters (Table 5), and tumor pathological features (Table 6) revealed no significant differences between groups (all P > 0.05).

Survival analysis by duration of analgesic administration

Kaplan-Meier analyses revealed significantly improved survival in patients with ≤ 5 days of analgesic administration compared to > 5 days (P = 0.003) (Figure 1A). Consistent patterns were observed for both opioid (P = 0.019) (Figure 1B) and nonsteroidal anti-inflammatory drug (NSAID) administration (P = 0.028) (Figure 1C).

Multivariate analysis using perioperative Cox proportional hazards model for overall survival

After adjusting for potential confounding variables (P ≤ 0.1 in univariate analysis), TNM stage (HR = 2.31, 95%CI: 1.72-3.10, P < 0.001), tumor differentiation (moderate: HR = 1.46, 95%CI: 1.02-2.09, P = 0.038; poor: HR = 2.15, 95%CI: 1.47-3.14, P < 0.001), and extended analgesic administration (> 5 days) (HR = 1.43, 95%CI: 1.08-1.89, P = 0.012) emerged as independent predictors of decreased survival (Table 7).

DISCUSSION

Our multivariate Cox proportional hazards analysis identified TNM stage, tumor differentiation, and extended post-operative analgesic administration as independent prognostic factors in patients with esophageal cancer. Advanced TNM stage (III/IV) significantly increased mortality risk (HR = 2.31, 95%CI: 1.72-3.10, P < 0.001) compared to stage I/II, aligning with previous findings[14]. The prognostic value of TNM staging was further validated by univariate analysis, which demonstrated that its components - tumor size, invasion depth, and lymph node status - all correlated with survival. The depth of tumor invasion represents a critical prognostic determinant, particularly given the distinct

Table 1 Univariate Cox analysis of baseline characteristics for overall survival, *n* (%)

Baseline characteristic	*n* = 378	Hazard ratio	95%CI	*P* value
Age				
<65 years	215 (56.88)	1.00	Reference	-
≥ 65 years	163 (43.12)	1.52	1.18-1.96	0.001
Gender				
Male	292 (77.25)	1.00	Reference	-
Female	86 (22.75)	0.89	0.67-1.19	0.44
BMI (kg/m²), mean ± SD	23.10 ± 3.20	0.97	0.93-1.02	0.24
Hypertension				
No	246 (65.08)	1.00	Reference	-
Yes	132 (34.92)	1.28	0.99-1.65	0.06
Diabetes				
No	298 (78.84)	1.00	Reference	-
Yes	80 (21.16)	1.31	0.98-1.75	0.07
Smoking history				
No	156 (41.27)	1.00	Reference	-
Yes	222 (58.73)	1.22	0.94-1.58	0.13
History of drinking				
No	169 (44.70)	1.00	Reference	-
Yes	209 (55.29)	1.15	0.89-1.48	0.28
Chronic gastritis				
No	271 (71.69)	1.00	Reference	-
Yes	107 (28.31)	1.12	0.85-1.47	0.43
ASA classification				
III	312 (82.54)	1.00	Reference	-
IV	66 (17.46)	1.45	1.08-1.95	0.01
NYHA classification				
I	256 (67.72)	1.00	Reference	-
II	89 (23.54)	1.33	0.99-1.78	0.06
III	33 (8.74)	1.68	1.12-2.52	0.01
Glomerular filtration rate				
< 90 mL/minute/1.73 m²	142 (37.57)	1.00	Reference	-
≥ 90 mL/minute/1.73 m²	236 (62.43)	0.81	0.63-1.05	0.11

CI: Confidence interval; BMI: Body mass index; ASA: American Society of Anesthesiologists; NYHA: New York Heart Association.

anatomical structure of the esophagus[15]. The absence of serosa and the relatively thin esophageal wall facilitate rapid transmural invasion; consequently, once tumors penetrate the muscularis propria, the risk of both locoregional infiltration and distant dissemination increases markedly. Lymph node metastasis significantly impacts prognosis by reflecting tumor invasiveness and metastatic potential, facilitating tumor spread through disruption of local immune barriers, and necessitating more extensive surgery with increased risk of surgical trauma and complications[16-18].

Tumor differentiation emerged as another crucial prognostic indicator, with both moderate (HR = 1.46, 95%CI: 1.02-2.09, $P = 0.038$) and poor differentiation (HR = 2.15, 95%CI: 1.47-3.14, $P < 0.001$) associated with inferior outcomes. This gradient relationship likely reflects the enhanced invasiveness, complex molecular alterations, and treatment resistance of poorly differentiated tumors[19,20]. The independent prognostic value of TNM stage and differentiation suggests they capture distinct aspects of tumor biology-anatomical progression and biological behavior, respectively. The integration of

Table 2 Univariate Cox analysis of surgery-related factors for overall survival, *n* (%)

Surgery-related factors	*n* = 378	Hazard ratio	95%CI	*P* value
Type of anesthesia				
General anesthesia	203 (53.70)	1.00	Reference	-
Epidural anesthesia	175 (46.30)	0.92	0.71-1.19	0.52
Surgical methods				
Open surgery	245 (64.81)	1.00	Reference	-
Minimally invasive surgery	133 (35.19)	0.78	0.60-1.02	0.07
Location of anastomotic site				
Cervical	228 (60.32)	1.00	Reference	-
Thoracic	150 (39.68)	1.25	0.97-1.62	0.09
Operative time, minutes, mean ± SD	266.01 ± 83.13	1.00	0.99-1.01	0.05
Duration of analgesic use				
≤ 5 days	149 (39.42)	1.00	Reference	-
> 5 days	229 (60.58)	1.62	1.24-2.12	< 0.001
Postoperative radiotherapy or chemotherapy				
No	198 (52.38)	1.00	Reference	-
Yes	180 (47.62)	1.45	1.12-1.88	0.01
Postoperative pneumonia				
No	265 (70.11)	1.00	Reference	-
Yes	113 (29.89)	1.58	1.21-2.06	0.001
Postoperative pleural effusion				
No	284 (75.13)	1.00	Reference	-
Yes	94 (24.87)	1.42	1.07-1.88	0.02

CI: Confidence interval.

Table 3 Univariate Cox analysis of pathological characteristics for overall survival, *n* (%)

Pathological characteristic	*n* = 378	Hazard ratio	95%CI	*P* value
TNM stage				
I or II stage	167 (44.18)	1.00	Reference	-
III or IV stage	211 (55.82)	2.85	2.15-3.78	< 0.001
Tumor location				
Upper segment	72 (19.05)	1.00	Reference	-
Middle segment	198 (52.38)	0.92	0.66-1.28	0.62
Lower segment	108 (28.57)	0.88	0.61-1.27	0.50
Tumor diameter				
< 3 cm	156 (41.27)	1.00	Reference	-
≥ 3 cm	222 (58.73)	1.68	1.29-2.19	< 0.001
Depth of tumor infiltration				
On the muscle layer	143 (37.83)	1.00	Reference	-
Subcutaneous muscle layer	235 (62.17)	1.92	1.46-2.52	< 0.001

Histological differentiation				
Well differentiated	89 (23.54)	1.00	Reference	-
Moderately differentiated	196 (51.85)	1.58	1.12-2.23	0.01
Poorly differentiated	93 (24.61)	2.42	1.67-3.51	< 0.001
Perineural invasion				
No	286 (75.66)	1.00	Reference	-
Yes	92 (24.34)	1.75	1.33-2.30	< 0.001
Tumor thrombus				
No	301 (79.63)	1.00	Reference	-
Yes	77 (20.37)	1.89	1.42-2.52	< 0.001
Lymph node metastasis				
No	184 (48.68)	1.00	Reference	-
Yes	194 (51.32)	2.32	1.77-3.04	< 0.001

CI: Confidence interval; TNM: Tumor-node-metastasis.

Table 4 Patient characteristics by analgesic use duration after esophagectomy, *n* (%)

Baseline characteristic	Short-term analgesic use (*n* = 149)	Long-term analgesic use (*n* = 229)	*t* value or χ^2	*P* value
Age			5.87	0.02
< 65 years	96 (64.43)	118 (51.53)		
≥ 65 years	53 (35.57)	111 (48.47)		
Gender			0.22	0.64
Male	117 (78.52)	175 (76.42)		
Female	32 (21.48)	54 (23.58)		
BMI (kg/m^2), mean ± SD	23.25 ± 3.15	23.01 ± 3.24	0.72	0.47
Hypertension			0.64	0.42
No	107 (71.81)	139 (60.70)		
Yes	42 (28.19)	90 (39.30)		
Diabetes			0.55	0.46
No	126 (84.56)	172 (75.11)		
Yes	23 (15.44)	57 (24.89)		
Smoking history			0.74	0.39
No	66 (44.30)	90 (39.30)		
Yes	83 (55.70)	139 (60.70)		
History of drinking			0.89	0.35
No	71 (47.65)	98 (42.79)		
Yes	78 (52.35)	131 (57.21)		
Chronic gastritis			0.52	0.47
No	104 (69.80)	167 (72.93)		
Yes	45 (30.20)	62 (27.07)		
ASA classification			0.65	0.42
III	133 (89.26)	179 (78.17)		
IV	16 (10.74)	50 (21.83)		

NYHA classification			1.24	0.54
I	108 (72.48)	148 (64.63)		
II	34 (22.82)	55 (24.02)		
III	7 (4.70)	26 (11.35)		
Glomerular filtration rate			2.24	0.14
< 90 mL/minute/1.73 m²	50 (33.56)	92 (40.17)		
≥ 90 mL/minute/1.73 m²	99 (66.44)	137 (59.83)		

CI: Confidence interval; BMI: Body mass index; ASA: American Society of Anesthesiologists; NYHA: New York Heart Association.

Table 5 Surgery-related factors by analgesic use duration after esophagectomy, *n* (%)

Surgery-related factors	Short-term analgesic use (*n* = 149)	Long-term analgesic use (*n* = 229)	*t* value or χ^2	*P* value
Type of anesthesia			0.33	0.57
General anesthesia	77 (51.68)	126 (55.02)		
Epidural anesthesia	72 (48.32)	103 (44.98)		
Surgical methods			1.96	0.17
Open surgery	83 (55.70)	162 (70.74)		
Minimally invasive surgery	66 (44.30)	67 (29.26)		
Location of anastomotic site			1.34	0.25
Cervical	78 (52.35)	150 (65.50)		
Thoracic	71 (47.65)	79 (34.50)		
Operative time, minutes, mean ± SD	265.83 ± 76.28	266.35 ± 85.42	1.73	0.09
Duration of analgesic use			2.74	0.10
≤ 5 days	85 (57.05)	113 (49.34)		
> 5 days	64 (42.95)	116 (50.66)		
Postoperative radiotherapy or chemotherapy			1.84	0.18
No	118 (79.19)	147 (64.19)		
Yes	31 (20.81)	82 (35.81)		
Postoperative pneumonia			1.95	0.16
No	122 (81.88)	162 (70.74)		
Yes	27 (18.12)	67 (29.26)		

CI: Confidence interval.

both TNM staging and tumor differentiation may provide more comprehensive prognostic stratification and guide therapeutic decision-making. Specifically, patients with early-stage disease but poor differentiation may benefit from intensified multimodal therapy, whereas selected patients with advanced-stage but well-differentiated tumors might remain candidates for surgical intervention, provided they meet appropriate physiological criteria for operability.

Notably, extended postoperative analgesic administration (> 5 days) independently predicted decreased survival (HR = 1.43, 95%CI: 1.08-1.89, P = 0.012), validating previous findings that reported a comparable hazard ratio (HR = 1.38) for extended analgesic use in gastrointestinal cancer patients[21]. Kaplan-Meier analyses demonstrated significantly decreased survival with prolonged administration of both opioids (P = 0.019) and NSAIDs (P = 0.028). Several mechanisms may explain this association:

Firstly, extended analgesic requirements may indicate complicated recovery, particularly in elderly patients who constituted a larger proportion of the > 5 days group (48.47% *vs* 35.57%, P = 0.015). Secondly, regarding opioid administration, our findings support the expanding evidence suggesting that opioids may influence tumor progression[22]. Recent molecular studies have demonstrated that opioids enhance tumor angiogenesis and suppress apoptosis through μ-opioid receptor activation[23]. The immunosuppressive effects of opioids, specifically on natural killer cell activity and T lymphocyte function[24], may explain the increased early recurrence risk observed in our study. Thirdly, our results

Table 6 Pathological characteristics by analgesic use duration after esophagectomy, *n* (%)

Pathological characteristic	Short-term analgesic use (*n* = 149)	Long-term analgesic use (*n* = 229)	*t* value or χ^2	*P* value
TNM stage			1.90	0.17
I or II stage	78 (52.35)	88 (38.43)		
III or IV stage	71 (47.65)	141 (61.57)		
Tumor location			0.16	0.92
Upper segment	29 (19.46)	43 (18.78)		
Middle segment	77 (51.68)	121 (52.84)		
Lower segment	43 (28.86)	65 (28.38)		
Tumor diameter			1.40	0.24
< 3 cm	74 (49.66)	81 (35.37)		
≥ 3 cm	75 (50.34)	148 (64.63)		
Depth of tumor infiltration			1.13	0.29
On the muscle layer	65 (43.62)	78 (34.06)		
Subcutaneous muscle layer	84 (56.38)	151 (65.94)		
Histological differentiation			2.74	0.26
Well differentiated	42 (28.19)	47 (20.52)		
Moderately differentiated	81 (54.36)	115 (50.22)		
Poorly differentiated	26 (17.45)	67 (29.26)		
Perineural invasion			1.49	0.22
No	124 (83.22)	162 (70.74)		
Yes	25 (16.78)	67 (29.26)		
Tumor thrombus			1.22	0.27
No	125 (83.89)	176 (76.86)		
Yes	24 (16.11)	53 (23.14)		
Lymph node metastasis			1.90	0.17
No	86 (57.72)	98 (42.79)		
Yes	63 (42.28)	131 (57.21)		

CI: Confidence interval; TNM: Tumor-node-metastasis.

indicate that extended postoperative administration may be detrimental. This aligns with Zhao-Fleming *et al*'s research [25], which demonstrated that prolonged NSAID use can result in complications affecting overall recovery. Furthermore, our observations support the findings of Arron *et al*[26], who documented increased surgical site complications with extended NSAID use, potentially compromising long-term outcomes.

These findings collectively suggest that optimizing perioperative pain management requires precise balance between adequate pain control and minimizing the potential adverse impacts of extended analgesic administration. This perspective aligns with recent guidelines recommending multimodal analgesic approaches to minimize the duration of both opioid and NSAID exposure while maintaining effective pain control[27].

Several limitations warrant consideration in this investigation. Primarily, the single-center retrospective design introduces potential selection bias, despite stringent inclusion and exclusion criteria. The institutional source limitation may affect the external validity and generalizability of our findings. Additionally, the retrospective methodology inherently presents challenges in data collection, particularly regarding critical perioperative parameters such as intraoperative blood loss and precise analgesic dosing, potentially affecting our analytical accuracy. Furthermore, while we identified an association between extended postoperative analgesic administration and adverse outcomes, the causal relationship remains uncertain due to potential unmeasured confounding variables, including underlying complications or compromised physical status that might independently influence prognosis. Lastly, the relatively brief follow-up period may inadequately capture long-term survival outcomes.

Future research directions should address these limitations through: (1) Implementation of multicenter, prospective trials with expanded cohorts and comprehensive perioperative data collection, particularly regarding pharmacological

Table 7 Multivariate analysis of survival-related factors in radically resected esophageal squamous cell carcinoma, *n* (%)

Variables	Hazard ratio	95%CI	*P* value
TNM staging	-	-	-
Phase I and II	1.00	Reference	-
Phase III and IV	2.31	1.72-3.10	< 0.001
Degree of tumor differentiation	-	-	-
Well differentiated	1.00	Reference	-
Moderately differentiated	1.46	1.02-2.09	0.038
Poorly differentiated	2.15	1.47-3.14	< 0.001
Postoperative analgesics used for more than 5 days	-	-	-
≤ 5 days	1.00	Reference	-
> 5 days	1.43	1.08-1.89	0.012

CI: Confidence interval; TNM: Tumor-node-metastasis.

interventions; (2) Mechanistic studies investigating analgesic-mediated effects on prognosis, emphasizing molecular biological pathways; (3) Development of individualized perioperative analgesic protocols that optimize pain management while minimizing adverse prognostic implications; and (4) Extended follow-up periods to evaluate the long-term impact of perioperative factors on survival outcomes. Moreover, integration of genomic and immunological profiling may provide deeper insights into prognostic determinants, facilitating the advancement of precision medicine approaches.

CONCLUSION

In conclusion, this comprehensive analysis demonstrates that TNM staging, tumor differentiation, and duration of postoperative analgesic administration serve as independent prognostic indicators in patients undergoing radical esophagectomy for esophageal carcinoma. These findings emphasize the critical importance of judicious perioperative analgesic management and the optimization of comprehensive perioperative care protocols. The implementation of evidence-based strategies in perioperative management may significantly influence clinical outcomes in this patient population. Further investigation into these prognostic determinants may facilitate the development of more individualized therapeutic approaches and ultimately enhance patient survival outcomes.

FOOTNOTES

Author contributions: Xu XJ and Liu SG contributed equally to the study design, data collection, and manuscript drafting, they contributed equally to this article, they are the co-first authors of this manuscript; He M and Zhao JD participated in surgical procedures, data analysis, and clinical interpretation; Pei L supervised the study, revised the manuscript, and oversaw submission; and all authors thoroughly reviewed and endorsed the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Machine learning-based prediction of postoperative mortality risk after abdominal surgery

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Abstract

BACKGROUND

Preoperative risk assessments are vital for identifying patients at high risk of postoperative mortality. However, traditional scoring systems can be time consuming. We hypothesized that the use of machine learning models would enable rapid and accurate risk assessments to be performed.

AIM

To assess the potential of machine learning algorithms to develop predictive models of mortality risk after abdominal surgery.

METHODS

This retrospective study included 230 individuals who underwent abdominal surgery at the Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine between January 2023 and December 2023. Demographic and surgery-related data were collected and used to develop nomogram, decision-tree, random-forest, gradient-boosting, support vector machine, and naïve Bayesian

models to predict 30-day mortality risk after abdominal surgery. Models were assessed using receiver operating characteristic curves and compared using the DeLong test.

RESULTS

Of the 230 included patients, 52 died and 178 survived. Models were developed using the training cohort (n = 161) and assessed using the validation cohort (n = 68). The areas under the receiver operating characteristic curves for the nomogram, decision-tree, random-forest, gradient-boosting tree, support vector machine, and naïve Bayesian models were 0.908 [95% confidence interval (CI): 0.824-0.992], 0.874 (95%CI: 0.785-0.963), 0.928 (95%CI: 0.869-0.987), 0.907 (95%CI: 0.837-0.976), 0.983 (95%CI: 0.959-1.000), and 0.807 (95%CI: 0.702-0.911), respectively.

CONCLUSION

Nomogram, random-forest, gradient-boosting tree, and support vector machine models all demonstrate strong performances for the prediction of postoperative mortality and can be selected based on the clinical circumstances.

Key Words: Abdominal surgery; Postoperative death; Prediction; Machine learning; Risk assessment

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Core Tip: Individuals vary in terms of surgical risk, and assessments must be performed to evaluate this risk in order to provide all patients with the most appropriate perioperative care. Current risk assessments can be time consuming; we therefore aimed to use artificial intelligence to develop a model to predict the risk of 30-day mortality in patients undergoing abdominal surgery. Data from patients that underwent abdominal surgery in our hospital were used to construct six separate models with different machine learning algorithms. Four of the models demonstrated strong predictive performance, suggesting their potential clinical application.

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INTRODUCTION

The rapid progress in modern medicine has increased the use of surgical interventions in the treatment of diseases. Currently, over 60 million people are admitted to Chinese healthcare facilities as inpatients each year, and this figure is rising. Optimal perioperative care is dependent on the use of accurate preoperative risk assessments to quickly identify high-risk patients and provide timely interventions. Consideration of risk factors allows the formulation of personalized patient management plans, enabling the efficient allocation of healthcare resources. This strategy significantly reduces the likelihood of postoperative complications and mortality[1,2]. Traditional preoperative risk assessments rely heavily on statistical scoring systems, which can be time consuming. There is therefore a pressing need for a rapid and objective method to assess and predict surgical risk. Over the past few years, remarkable progress has been made in the use of artificial intelligence (AI) in numerous fields, especially healthcare. Innovations in wearable technology, intelligent healthcare systems, medical imaging analysis, genetic data mining, biotechnological applications, health management, and risk prediction have changed conventional medical models and spurred advancements in contemporary medicine[3,4]. Machine learning, a key component of AI, has the potential to analyze vast medical datasets[5,6]. In the context of mortality risk prediction, machine learning is primarily concerned with enhancing model accuracy[7]. The present study utilized an extensive hospital data research platform to identify patients who died following abdominal surgery performed under general anesthesia. Comparing the data of patients who died and those who survived using logistic regression analyses identified significant risk factors. The primary objective of this study was to construct a predictive model of 30-day mortality risk in patients undergoing abdominal surgery using six of the most prevalent ensemble learning algorithms. This study aimed to offer innovative insights into the early detection of high-risk patients to facilitate targeted interventions.

MATERIALS AND METHODS

Patients

Individuals who underwent initial abdominal surgery under general anesthesia at the Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine between January 2023 and December 2023 were considered for inclusion in this study. The inclusion criteria were as follows: (1) Various types of abdominal surgeries, including liver,

gallbladder, pancreas, spleen, gastrointestinal, and colorectal surgeries, performed under general anesthesia; and (2) Death, if it occurred, occurred in hospital after surgery. The exclusion criteria were as follows: (1) Non-abdominal surgeries; (2) Procedures not performed under general anesthesia; (3) Preoperative occurrence of cardiac or respiratory arrest, and (4) Vital medical documentation missing or incomplete. This study was reviewed and approved by the Institutional Review Board of the Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine.

Data collection

Data on the time of death of the included patients were collected, as were data on factors at admission that could impact patient prognosis, including sex; age; body mass index; whether emergency surgery was performed; previous abdominal surgeries; smoking history; drinking history; presence of hypertension or diabetes; surgical approach; American Society of Anesthesiologists (ASA) classification; abnormal electrocardiogram findings; preoperative complications; systolic blood pressure; diastolic blood pressure; prothrombin time; activated partial thromboplastin time (APTT); albumin/globulin ratio; levels of D-dimer, fibrinogen, aspartate aminotransferase (AST), blood urea nitrogen, total bile acid, albumin, blood creatinine, total bilirubin (TBIL), blood calcium, blood sodium, blood potassium, and hemoglobin; counts of blood neutrophils, lymphocytes, white blood cells (WBC), and platelets; operation type; and operation duration.

Model construction and validation

R software (The R Foundation for Statistical Computing, Vienna, Austria) was used to construct the predictive models. The patients were randomly allocated to training (n = 161) or validation (n = 69) cohorts at a ratio of 7:3. Data from the training cohort were used to develop a model, and data from the validation cohort were used to assess its predictive capabilities. The dependent variable of the model was mortality within 30 days of the surgical intervention. The predictive ability of the model was evaluated by determining its accuracy, sensitivity, specificity, recall, precision, and area under the receiver operating characteristic (ROC) curve (AUC). The R packages "rms", "rpart", "randomForest", "gbm", and "e1071" were used to create nomogram (rms), decision-tree (rpart), random-forest (randomForest), gradient-boosting tree (gbm), support vector machine (e1071) and naive Bayes (e1071) models, respectively.

Statistical analysis

Statistical analyses were performed using statistical product and service solutions software version 23.0 (IBM Corporation, Armonk, NY, United States). Normally distributed measurement data are expressed as the mean ± SD, and a t-test was used to compare the groups. Categorical data are expressed as percentages, with group comparisons made using the χ^2 test. The closer the AUC value was to 1, the higher the accuracy of the diagnostic test; the AUC for each model was compared using the DeLong test. Statistical significance was defined as $P < 0.05$.

RESULTS

Univariate analysis

Of the 230 patients included in the study, 52 (22.61%) died within 30 days after surgery (death group) and 178 (77.39%) survived this period (survival group). The two groups differed significantly in terms of age, surgical approach, ASA classification, preoperative complications, APTT, AST level, TBIL level, and WBC count ($P < 0.05$). The remaining factors analyzed did not significantly differ between the two groups ($P > 0.05$), as presented in Table 1.

Multivariate analysis

Multivariate logistic regression analysis was performed using the binary outcome of survival for 30 days post-surgery as the dependent variable, where 1 signified death and 0 signified survival. Variables that demonstrated statistical significance in the univariate analysis were incorporated into the multivariate logistic regression model. Categorical variables were coded as follows: Surgical approach (laparoscopic surgery = 1, laparotomy/conversion to laparotomy = 2), ASA classification (I = 1, II = 2, III = 3, IV = 4, and V = 5), and preoperative complications (yes = 1, no = 0). The actual numerical values were entered for continuous variables, including age, APTT, AST level, TBIL level, and WBC count. Age, APTT, AST level, TBIL level, and WBC count were identified as significant predictors of postoperative mortality in patients who underwent abdominal surgery ($P < 0.05$), as shown in Table 2. The predictive model was formulated, based on the results of the multivariate regression analysis, as Y = 4.880 - 0.609 (age) + 0.533 (APTT) + 0.172 (AST level) + 0.174 (TBIL level) + 0.183 (WBC count). For example, for every unit increase in the patient's APTT value, the log odds ratio (OR) of postoperative death increases by 0.533 (β = 0.533), and the risk of death increases by 1.705 times [OR = 1.705; 95% confidence interval (CI): 1.379-2.107].

ROC curve of predictive ability

The ROC curve of the ability of the constructed model to predict the risk of postoperative mortality in patients who underwent abdominal surgery is presented in Figure 1. The AUC was 0.942, with a 95%CI ranging from 0.910 to 0.975. On the ROC curve, the comprehensive performance of the model can reach a relatively optimal threshold point. The optimal threshold was identified as -0.165, which was associated with a sensitivity (the proportion of those correctly diagnosed as ill) of 0.923 and a specificity (the proportion of individuals correctly diagnosed as healthy) of 0.899.

Table 1 Univariate analysis of postoperative death in patients undergoing abdominal surgery, mean ± SD/*n* (%)

Index	Death (*n* = 52)	Survival (*n* = 178)	t/χ^2	*P* value
Sex			0.025	0.875
Male	27 (51.92)	95 (53.37)		
Female	25 (48.08)	83 (46.63)		
Age, years	59.21 ± 5.26	57.34 ± 6.14	1.990	0.048
BMI, kg/m^2	23.50 ± 2.73	23.89 ± 2.95	-0.839	0.403
Emergency surgery			1.525	0.217
Yes	19 (36.54)	48 (26.97)		
No	33 (63.46)	130 (73.03)		
Previous abdominal surgery			0.073	0.787
Yes	14 (26.92)	45 (25.28)		
No	38 (73.08)	133 (74.72)		
Smoking			0.303	0.582
Yes	10 (19.23)	40 (22.47)		
No	42 (80.77)	138 (77.53)		
Drinking			0.014	0.904
Yes	24 (46.15)	81 (45.51)		
No	28 (53.85)	97 (54.49)		
Hypertension			0.115	0.735
Yes	5 (9.62)	19 (10.67)		
No	47 (90.38)	159 (89.33)		
Diabetes			0.031	0.861
Yes	18 (34.62)	59 (33.15)		
No	34 (65.38)	119 (66.85)		
Surgical approach			7.209	0.007
Laparoscopic	23 (44.23)	111 (62.36)		
Laparotomy/conversion	29 (55.77)	67 (37.64)		
ASA classification			10.011	0.040
I	3 (5.77)	9 (5.06)		
II	27 (51.92)	130 (73.03)		
III	12 (23.08)	26 (14.61)		
IV	9 (17.31)	8 (4.49)		
V	1 (1.92)	5 (2.81)		
Abnormal ECG			1.792	0.181
Yes	27 (51.92)	73 (41.01)		
No	25 (48.08)	105 (58.99)		
Preoperative complications			8.136	0.004
Yes	16 (30.77)	26 (14.61)		
No	36 (69.23)	152 (85.39)		
SBP, mmHg	127.94 ± 7.53	128.59 ± 6.04	-0.642	0.522
DBP, mmHg	74.44 ± 5.27	75.20 ± 6.15	-0.809	0.420
D-dimer, mg/L	1.18 ± 0.35	1.13 ± 0.20	1.120	0.264

PT, second	12.29 ± 3.15	11.90 ± 2.38	0.948	0.344
APTT, second	32.33 ± 2.83	27.04 ± 3.46	10.077	< 0.001
FBG, g/L	3.31 ± 0.74	3.38 ± 0.89	-0.503	0.616
AST, IU/L	43.50 ± 14.51	37.46 ± 9.72	3.489	0.001
BUN, mmol/L	5.63 ± 0.63	5.53 ± 0.69	0.993	0.322
TBA, μmol/L	10.55 ± 2.32	10.12 ± 1.96	1.323	0.187
ALB, g/L	34.99 ± 5.94	35.81 ± 5.45	-0.934	0.351
A/G ratio	1.24 ± 0.29	1.32 ± 0.27	-1.800	0.073
Cre, μmol/L	69.61 ± 9.07	68.25 ± 8.09	1.036	0.301
TBIL, μmol/L	26.07 ± 3.82	20.38 ± 4.42	8.400	< 0.001
Blood calcium, mmol/L	2.17 ± 0.14	2.16 ± 0.17	0.447	0.655
Blood sodium, mmol/L	140.13 ± 3.35	140.98 ± 3.29	-1.654	0.099
Blood potassium, mmol/L	3.82 ± 0.38	3.81 ± 0.40	0.103	0.918
NEUT, × 10^9/L	5.13 ± 0.79	4.98 ± 0.56	1.486	0.139
LYMPH, × 10^9/L	1.21 ± 0.25	1.28 ± 0.33	-1.393	0.165
WBC, × 10^9/L	11.84 ± 3.94	9.72 ± 3.44	3.774	< 0.001
PLT, × 10^9/L	191.35 ± 63.09	194.91 ± 50.82	-0.420	0.675
Hb, g/L	116.75 ± 5.89	116.40 ± 5.78	0.384	0.701
Operation type				
Emergency	2 (3.85)	1 (0.56)	3.104	0.541
Urgent	9 (17.31)	36 (20.22)		
Semi-urgent	12 (23.08)	45 (25.28)		
Non-urgent	11 (21.15)	28 (15.73)		
Elective	18 (34.62)	68 (38.20)		
Operation time, hour	2.52 ± 1.09	2.54 ± 1.03	-0.103	0.918

BMI: Body mass index; ECG: Electrocardiogram; ASA: American Society of Anesthesiologists; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PT: Prothrombin time; APTT: Activated partial thromboplastin time; FBG: Fibrinogen; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; TBA: Total bile acid; ALB: Albumin; A/G: Albumin/globulin ratio; Cre: Creatinine; TBIL: Total bilirubin; NEUT: Neutrophils; LYMPH: Lymphocytes; WBC: White blood cell; PLT: Platelets; Hb: Hemoglobin.

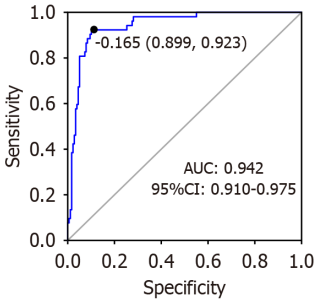


Figure 1 Receiver operating characteristic curve of the model to predict the risk of postoperative death in patients who underwent abdominal surgery. AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

Comparison of clinical data between the training set and validation set

Comparison of the training and validation cohorts showed no significant differences between the groups in terms of the identified predictors of postoperative mortality ($P < 0.05$) (Table 3).

Table 2 Multivariate logistic regression analysis of postoperative death in patients undergoing abdominal surgery

Index	B	SE	Wald	*P* value	OR	95%CI
Age	-0.609	0.146	17.291	< 0.001	0.544	0.408-0.725
Surgical approach	0.305	0.495	0.380	0.538	1.357	0.514-3.582
Preoperative complications	-0.172	0.605	0.081	0.776	0.842	0.257-2.753
APTT	0.533	0.108	24.360	< 0.001	1.705	1.379-2.107
AST	0.172	0.062	7.681	0.006	1.188	1.052-1.341
TBIL	0.174	0.078	4.962	0.026	1.190	1.021-1.387
ASA classification	0.119	0.300	0.158	0.691	1.127	0.626-2.030
WBC	0.183	0.074	6.154	0.013	1.201	1.039-1.388
Constant	4.880	5.475	0.794	0.373	131.566	

OR: Odds ratio; CI: Confidence interval; APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; TBIL: Total bilirubin; ASA: American Society of Anesthesiologists; WBC: White blood cell.

Table 3 Comparison of predictors between the training and validation cohorts, mean ± SD

Index	Training cohort (*n* = 161)	Validation cohort (*n* = 69)	*t*	*P* value
Age	57.67 ± 5.80	57.99 ± 6.46	-0.364	0.716
APTT	28.16 ± 4.00	28.41 ± 3.99	-0.424	0.672
AST	38.41 ± 10.75	39.80 ± 12.33	-0.860	0.391
TBIL	21.44 ± 4.75	22.20 ± 5.24	-1.081	0.281
WBC	10.33 ± 3.59	9.88 ± 3.84	0.856	0.393

APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; TBIL: Total bilirubin; WBC: White blood cell.

Nomogram construction and verification

Using the five significant predictors identified by multivariate logistic regression, a nomogram for postoperative mortality after abdominal surgery was developed using training cohort data (Figure 2). As an example, a patient aged 65 years, with an APTT of 32 seconds, an AST level of 60.23 IU/L, a TBIL level of 18.42 μmol/L, and a WBC count of 12 × 10^9/L, would be allocated nomogram scores of approximately 37, 26, 45, 7, and 9, respectively. This would result in a total score of 124, translating to a postoperative mortality risk of approximately 18%. ROC curve analysis revealed that the AUC for the ability of the nomogram to predict the likelihood of postoperative death in patients who underwent abdominal surgery was 0.943 (95%CI: 0.897-0.988), with a specificity of 0.904 and a sensitivity of 0.944, in the training cohort. For the validation cohort, the AUC was 0.908 (95%CI: 0.824-0.992), with a specificity of 0.925 and a sensitivity of 0.750, as presented in Figure 3A and B.

Decision-tree model construction and verification

A decision-tree model was established using the training cohort, as illustrated in Figure 4. As an example, a patient aged 58 years presenting with an APTT of 29 seconds and a WBC count of 14 × 10^9/L would have an estimated probability of postoperative mortality of 6%. ROC curve analysis indicated that the AUC for the decision-tree model was 0.930 (95%CI: 0.880-0.979), with a specificity of 0.920 and a sensitivity of 0.917. In the validation cohort, the AUC was 0.874 (95%CI: 0.785-0.963), with a specificity of 0.792 and a sensitivity of 0.938, as demonstrated in Figure 3C and D.

Random-forest model construction and verification

A random-forest model was developed using the training cohort to rank the variables influencing the risk of postoperative death in patients who underwent abdominal surgery, with the order of significance being the APTT, WBC count, TBIL level, AST level, and age (Figure 5). The higher the score, the greater the variable's influence on the predictive ability of the model. ROC curve analysis revealed that the AUC for the random-forest model was 1 (95%CI: 1-1), achieving a specificity of 1 and a sensitivity of 1. In the validation cohort, the AUC was 0.928 (95%CI: 0.869-0.987), with a specificity of 0.811 and a sensitivity of 1.000, as depicted in Figure 3E and F.

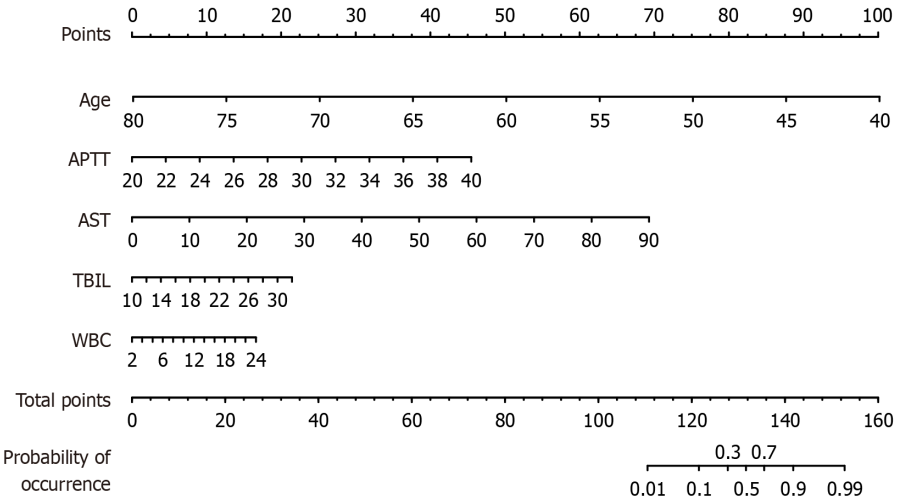


Figure 2 Nomogram for the risk of postoperative death in patients who underwent abdominal surgery. The independent influencing factors used in the process of establishing the model were derived from the multivariate logistic regression analysis. APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; TBIL: Total bilirubin; WBC: White blood cell.

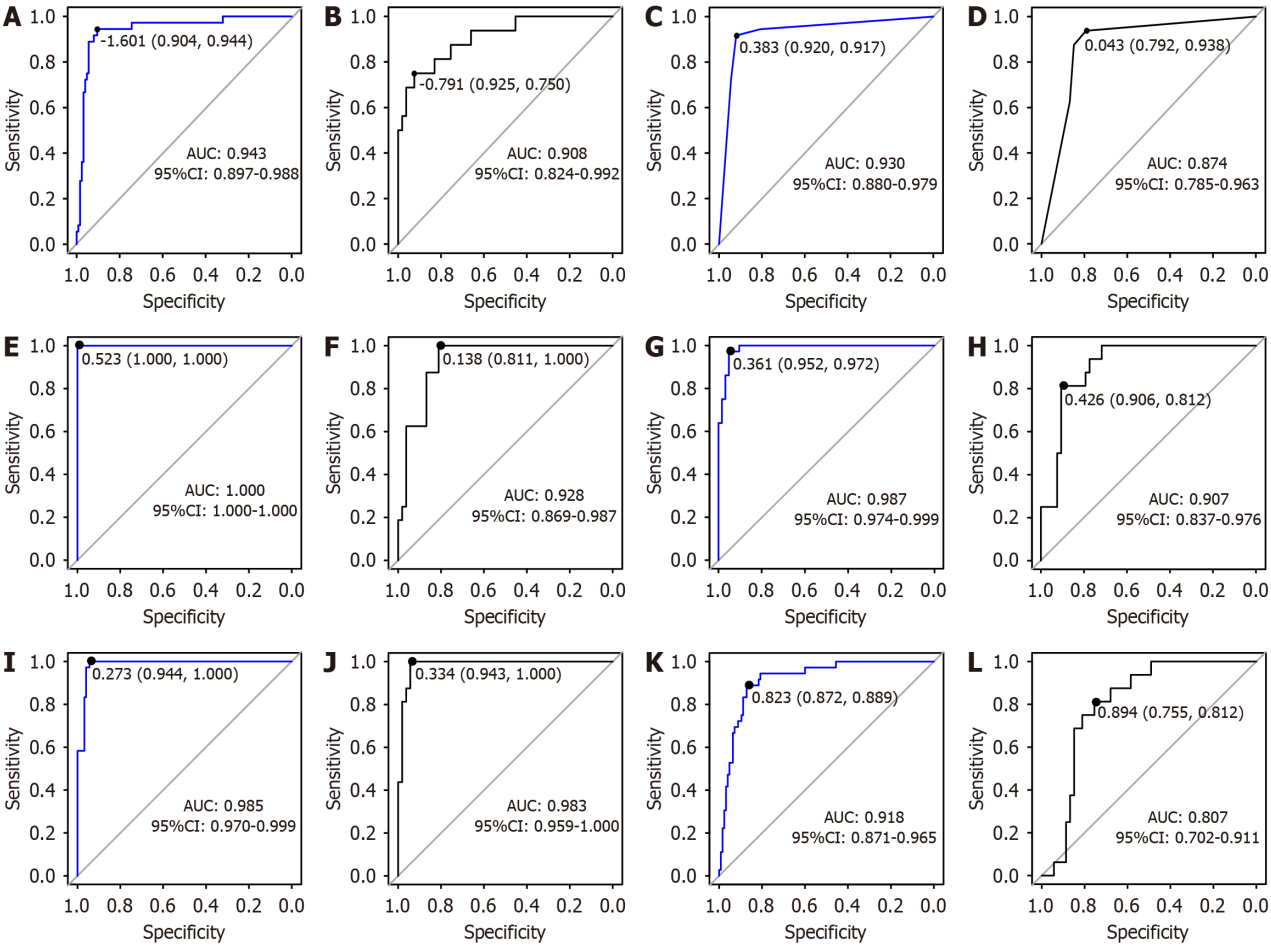


Figure 3 Receiver operating characteristic curves to predict postoperative death in patients who underwent abdominal surgery. A: The nomogram (training cohort); B: The nomogram (validation cohort); C: The decision-tree model (training cohort); D: The decision-tree model (validation cohort); E: The random-forest model (training cohort); F: The random-forest model (validation cohort); G: The gradient-boosting tree model (training cohort); H: The gradient-boosting tree model (validation cohort); I: The support vector machine model (training cohort); J: The support vector machine model (validation cohort); K: The naive Bayesian model (training cohort); L: The naive Bayesian model (validation cohort). AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

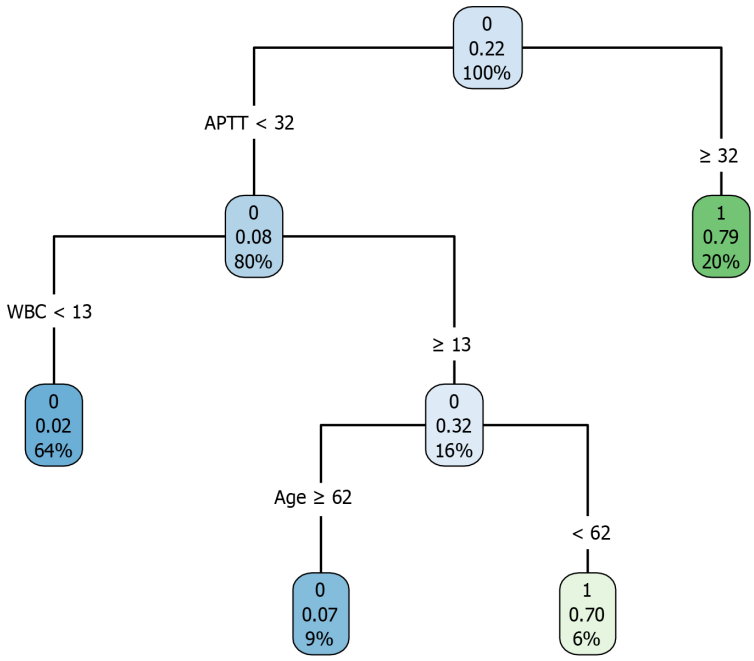


Figure 4 Decision-tree prediction model for the risk of postoperative death in patients who underwent abdominal surgery. The independent influencing factors used in the process of establishing the model were derived from the multivariate logistic regression analysis. APTT: Activated partial thromboplastin time; WBC: White blood cell.

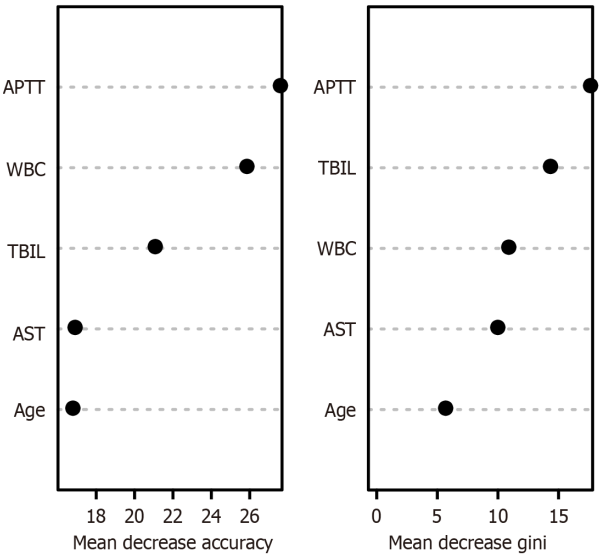


Figure 5 Random-forest prediction model for the risk of postoperative death in patients who underwent abdominal surgery. The independent influencing factors used in the process of establishing the model were derived from the multivariate logistic regression analysis. APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; TBIL: Total bilirubin; WBC: White blood cell.

Gradient-boosting tree model construction and verification

A gradient-boosting tree model was established using the training dataset to determine the relative significance of the five indicators ranked by the following importance scores: APTT (30.190), TBIL level (25.466), WBC count (24.170), AST level (12.340), and age (7.834), as illustrated in Figure 6. The higher the score, the greater the variable's influence on the predictive ability of the model. ROC curve analysis indicated that the AUC for the gradient-boosting tree model was 0.987 (95%CI: 0.974-0.999), with a specificity of 0.952 and a sensitivity of 0.972. In the validation cohort, the AUC was 0.907 (95%CI: 0.837-0.976), with a specificity of 0.906 and a sensitivity of 0.812, as presented in Figure 3G and H.

Support vector machine model construction and verification

A support vector machine model was constructed using the training dataset. The confusion matrix of the model is shown in Figure 7A. ROC curve analysis showed that the support vector machine model, when applied to the training cohort,

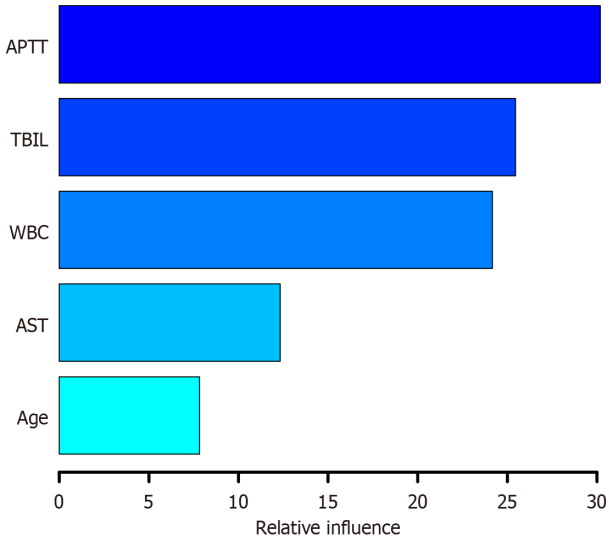


Figure 6 Gradient-boosting tree model for the risk of postoperative death in patients who underwent abdominal surgery. The independent influencing factors used in the process of establishing the model were derived from the multivariate logistic regression analysis. APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; TBIL: Total bilirubin; WBC: White blood cell.

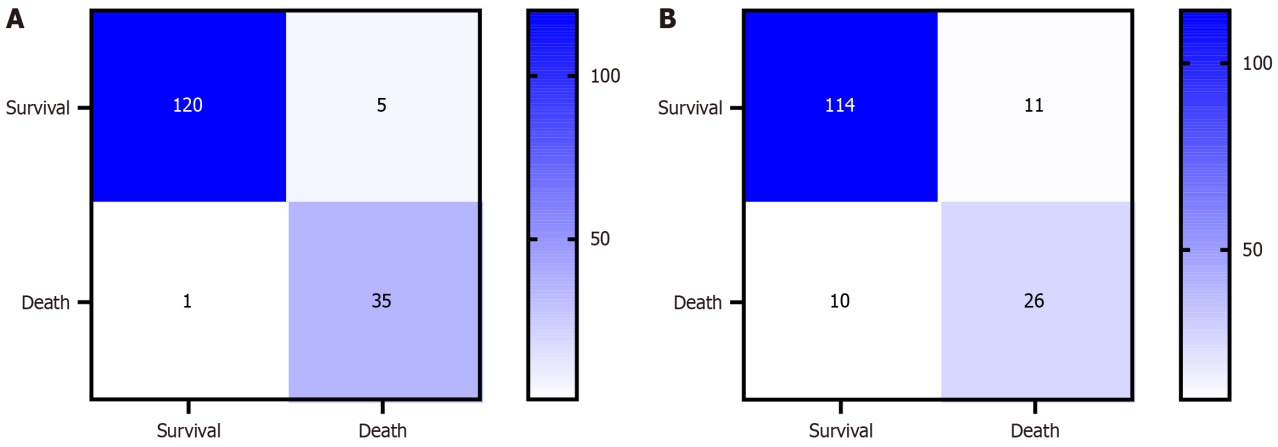


Figure 7 Confusion matrix for the risk of postoperative death in patients who underwent abdominal surgery. A: The support vector machine model; B: The naive Bayesian model. The independent influencing factors used in the process of establishing the model were derived from the multivariate logistic regression analysis.

demonstrated an AUC of 0.985 (95%CI: 0.970-0.999), with a specificity of 0.944 and a perfect sensitivity of 1.000. In the validation cohort, the AUC was 0.983 (95%CI: 0.959-1.000), with a specificity of 0.943 and a sensitivity that remained 1.000, as shown in Figure 3I and J.

Naive Bayesian model construction and verification

A naive Bayesian model was developed using the training cohort. The confusion matrix for this model is shown in Figure 7B. ROC curve analysis indicated that the AUC for the naive Bayesian model was 0.918 (95%CI: 0.871-0.965), with a specificity of 0.872 and a sensitivity of 0.889. In the validation cohort, the AUC was 0.807 (95%CI: 0.702-0.911), with a specificity of 0.755 and a sensitivity of 0.812, as depicted in Figure 3K and L.

Model performance comparison

The performances of the six models built with the training cohort were assessed using the validation cohort. The DeLong test revealed that the support vector machine model, with an AUC of 0.983 (95%CI: 0.959-1.000), outperformed the decision-tree model (P = 0.023), with an AUC of 0.874 (95%CI: 0.785-0.963), and the gradient-boosting tree model (P = 0.031), with an AUC of 0.907 (95%CI: 0.837-0.976). The naive Bayesian model, with an AUC of 0.807 (95%CI: 0.702-0.911), underperformed compared to the nomogram model (P = 0.021), with an AUC of 0.908 (95%CI: 0.824-0.992), the random-forest model (P = 0.049), with an AUC of 0.928 (95%CI: 0.869-0.987), the gradient-boosting tree model (P = 0.006), and the support vector machine model (P = 0.001); all these differences were statistically significant (P < 0.05). No significant differences were observed between the AUC pairs of the other models (P < 0.05). The accuracy (the proportion of the number of samples with correct predictions to the total number of samples), sensitivity, specificity, recall (true positive

rate), and precision (if the proportion of samples predicted as positive by the model is actually the proportion of positive cases) metrics of the six models are listed in Table 4.

DISCUSSION

Machine learning can learn from extensive datasets without explicit programming instructions. This technology enables the enhancement of performance over time[8-10]. In contrast, traditional medical electronic information systems aggregate patient data and process information based on predefined rules[11]. The use of machine learning in medicine allows for more in-depth data analysis than is possible with traditional analytical techniques, and therefore holds great promise for clinical use[12]. In this study, the ability of machine learning models to predict 30-day postoperative mortality following abdominal surgery was studied using six prominent algorithms.

The findings of this study indicate that age, APTT, TBIL level, AST level, and WBC count are predictive of postoperative mortality risk after abdominal surgery. The APTT is an indicator of coagulation status, and a longer APTT should be considered, especially when administering preoperative anticoagulants, which could lead to increased bleeding during and after surgery[13,14]. Postoperative bleeding is a significant contributor to mortality. Our findings support the notion that an extended APTT is associated with a heightened risk of postoperative death. Elevated TBIL levels are indicative of liver dysfunction in terms of its metabolic and excretory capabilities, and thus affects patient outcomes[15]. The present study revealed significantly higher TBIL levels in the death group than in the survival group, suggesting that the TBIL level is a significant risk factor for death after abdominal surgery. AST is predominantly found in the myocardium, liver, skeletal muscle, kidneys, and pancreas. In the context of abdominal surgery, and in particular liver procedures, AST may be released into the bloodstream due to liver damage, increasing serum AST levels[16,17]. This increase not only signifies liver injury and potential dysfunction, but may also be linked to postoperative complications, inflammation, and infections, all of which could increase the mortality risk. The WBC count is a crucial predictor of postoperative death in patients undergoing abdominal surgery, as it reflects the body's response to infection and inflammation[18,19]. An elevated WBC count typically signifies the presence of inflammation or infection, which, if left untreated, can lead to severe complications and potentially death after abdominal surgery[20]. Consequently, vigilant postoperative monitoring of the WBC count and prompt intervention are essential to minimize the mortality risk.

Medical data, which are characterized by heterogeneity, high dimensionality, intricate causality, imbalances, and gaps, present challenges for single machine learning algorithms in capturing complex relationships[21]. The integration of various machine learning algorithms has emerged as a novel approach in medical research. A 2020 study by Agius *et al* [22] combined 28 machine learning algorithms, including those used in the present study, to develop a new predictive algorithm for the risk of infection in patients undergoing standard treatment for chronic lymphoblastic leukemia, achieving a recall rate and accuracy exceeding 70%, an improvement over single models.

In the present study, six prevalent machine learning algorithms were selected for analysis. The findings indicated that nomogram, random-forest, gradient-boosting tree, and support vector machine models have strong predictive capabilities, with AUCs above 0.9, whereas the naive Bayes model did not show significant benefits. Liu *et al*[23] employed a support vector machine model to predict mucosal activity and surgical risk in patients with Crohn's disease. The obtained AUC was ideal and comparable to the results of the present study. However, the number of models utilized in their research was relatively limited, making it challenging to identify an accurate model with certainty. In contrast, Yan *et al*[24] utilized a variety of models to predict the risk of mortality following abdominal surgery. Nevertheless, their study relied on data from the American College of Surgeons National Surgical Quality Improvement Program, which may have limited applicability to local Chinese cases. In the early days of information technology, the costs associated with data collection, storage, and analysis were prohibitive, leading to the development of simple and streamlined models[25]. However, with economic growth and technological advancements, the costs of data collection and storage have diminished, and data analysis techniques have become more sophisticated[26]. Clinical prediction models can now access larger and more diverse datasets, and by leveraging increasingly complex technologies, such as machine learning and AI, they can provide more precise outcomes to serve the needs of physicians, patients, medical decision makers, government agencies, and health administrators[27].

CONCLUSION

In the context of perioperative care, precise risk assessments are crucial for clinical staff to promptly identify high-risk patients and initiate early interventions. Tailored nursing management strategies can be devised to address the identified risk factors, thereby potentially reducing the incidence of postoperative complications and mortality. This strategy also allows a more effective allocation of healthcare resources. The cases analyzed in the current study were exclusively Chinese; therefore, they more accurately reflect the actual clinical situation in China compared to cases evaluated in other studies. However, our study was limited to a single center, and the sample size was relatively small; this restricts its ability to represent the broader population of patients undergoing abdominal surgery across different regions, hospital levels, and medical teams. Although some models appear to perfectly differentiate between death and survival, their validity requires further scrutiny. In the future, we plan to conduct prospective studies with larger sample sizes to systematically collect data and mitigate issues associated with missing data or inaccurate records that are common in retrospective studies. Furthermore, we aim to gather extensive data from multi-regional and multi-level hospitals, covering a diverse range of patients undergoing abdominal surgery with varying ages, sexes, disease types, and severity

Table 4 Model prediction efficiency

Model	AUC (95%CI)	Accuracy	Sensitivity	Specificity	Recall	Precision
Nomogram	0.908 (0.824-0.992)	0.899	0.962	0.688	0.962	0.911
Decision-tree	0.874 (0.785-0.963)	0.855	0.849	0.875	0.849	0.957
Random-forest	0.928 (0.869-0.987)	0.841	0.906	0.625	0.906	0.889
Gradient-boosting tree	0.907 (0.837-0.976)	0.870	0.906	0.750	0.906	0.923
Support vector machine	0.983[a,2,4] (0.959-1.000)	0.884	0.925	0.750	0.925	0.925
Naive Bayes	0.807[a,1,3,4,5] (0.702-0.911)	0.797	0.811	0.750	0.811	0.915

[a]$P < 0.05$.
[1]P *vs* nomogram.
[2]P *vs* decision-tree model.
[3]P *vs* random-forest model.
[4]P *vs* gradient-boosting tree model.
[5]P *vs* support vector machine model.
AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

levels. These improvements are designed to enhance the generalizability of our models, ensure that our research findings are more universally applicable, and ultimately provide more robust guidance for clinical practice.

FOOTNOTES

Author contributions: Yuan JH and Jin YM contributed equally to this work as co-first authors; Yuan JH and Zhao B contributed to conception and design; Jin YM contributed to administrative support; Xiang JY contributed to provision of study materials; Li SS contributed to collection and assembly of data; Zhong YX contributed to data analysis and interpretation; Yuan JH, Jin YM, Xiang JY, Li SS, Zhong YX, Zhang SL, Zhao B contributed to manuscript writing and final approval of manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic submucosal dissection for esophageal precancerous lesions and early esophageal carcinoma: Analysis of efficacy and serum tumor markers

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Abstract

BACKGROUND

Tumor progression in patients with esophageal precancerous lesions (EPLs) or early esophageal carcinoma (EEC) is typically confined in both extent and location. Prompt and effective intervention significantly improves treatment outcomes and prognosis for these individuals.

AIM

To determine the effect of endoscopic submucosal dissection (ESD) on efficacy, serum tumor markers (STMs), and 6-month postoperative recurrence rate in patients with either EPL or EEC.

METHODS

This study initially enrolled 120 patients with EPL or EEC, who were admitted from April 2021 to April 2024. Participants were divided into the control group (60 cases), which underwent thoracotomy, and the research group (60 cases) which received ESD treatment. The comparative analysis involved information regarding the efficacy (dissection area and resection rate per unit time), complications (delayed bleeding, wound infection, esophageal reflux, and postoperative esophageal stenosis), surgery-related parameters (bleeding volume, operation duration, and hospital length of stay), STMs [carcinoembryonic antigen (CEA), carbohydrate antigen 724 (CA724), and tumor-specific growth factor (TSGF)], and the 6-month postoperative recurrence rate of the two groups.

RESULTS
Data indicated statistically higher dissection area and resection rate per unit of time in the research group than in the control group. Meanwhile, the research group demonstrated a notably lower overall incidence rate of complications, bleeding volume, operation duration, and hospital length of stay. Further, the CEA, CA724, and TSGF were markedly reduced in the research group after treatment, which were statistically lower compared to the baseline and those of the control group. Finally, during the follow-up, a comparable 6-month postoperative recurrence rate was determined in the two groups.

CONCLUSION
ESD is clinically effective and safe for EPL and EEC and can significantly restore abnormally increased levels of STMs.

Key Words: Endoscopic submucosal dissection; Esophageal precancerous lesions; Early esophageal carcinoma; Therapeutic efficacy; Serum tumor markers

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Core Tip: Studies on the efficacy of endoscopic submucosal dissection (ESD) in treating esophageal precancerous lesions (EPLs) or early esophageal carcinoma (EEC), as well as its effects on serum tumor markers (STMs) and the 6-month postoperative recurrence rate, remains limited. This study included 120 patients with EPL or EEC and compared the clinical outcomes of ESD with thoracotomy. The results indicate that ESD provides significant clinical advantages for these patients, including larger dissection area, higher resection rate per unit time, reduced risk of complications, less intraoperative bleeding, shorter operative duration, and accelerated recovery. Moreover, ESD effectively suppresses abnormal STM levels, such as carcinoembryonic antigen, carbohydrate antigen 724, and tumor-specific growth factor. These results provide comprehensive and robust clinical evidence to support the use of ESD in EPL and EEC management.

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INTRODUCTION

Esophageal carcinoma (EC), as a prevalent malignant neoplasm in the digestive tract, ranks as the sixth leading cause of cancer-related mortality globally[1]. Its etiological factors potentially involve smoking, alcohol consumption, low fruit and vegetable ingestion, gastroesophageal reflux, and predisposing genes, all of which may augment the risk of EC development[2]. Statistically, the 5-year survival rates of EC in the United States and China are 18.5% and 36.9%, respectively, demonstrating a poor prognosis, which is primarily related to the majority of patients being diagnosed at an advanced stage[3,4]. To improve the 5-year survival rate and the prognosis of patients with EC, early diagnosis and prompt intervention are of paramount significance[5]. The extent and location of tumor progression are circumscribed for patients with esophageal precancerous lesions (EPLs) and early EC (EEC), and effective intervention at this stage confers superior therapeutic efficacy and prognosis[6,7]. Endoscopic submucosal dissection (ESD) represents the treatment of choice for patients with EPL or EEC. Compared with conventional thoracotomy, ESD provides advantages such as less surgical trauma and esophageal physiological structure preservation. It enables *en-bloc* and complete lesion resection and contributes to reduced risk of distant metastasis[8-10]. Besides, this technique provides an *en-bloc* specimen; thus, it furnishes more detailed pathological information for risk stratification in esophageal diseases[11]. Ning *et al*[12] indicated that, when ESD is used to treat patients with EEC, it entails a low recurrence risk while enabling relatively high overall, R0, and radical resection rates. However, this surgical modality has certain disadvantages. Specifically, the risk of postoperative esophageal stenosis is as high as 70%–80% if the resection exceeds 75% of the circumference, and the risk approaches nearly 100% if the entire circumference is resected[13]. The present study primarily focuses on analyzing the effect of ESD on the efficacy of EPL and EEC treatment, serum tumor markers (STMs), and the six-month postoperative recurrence rate. Studies in this domain are scarce, and this research aims to provide more abundant and comprehensive clinical evidence and practical guidance.

MATERIALS AND METHODS

Patient information

This study included 120 patients with EPL or EEC, who visited the Affiliated Taizhou Second People's Hospital of Yangzhou University from April 2021 to April 2024. Of the participants, 60 underwent thoracotomy (control group) and 60 received ESD treatment (research group). The male-to-female ratios of the control and research groups were 43:17 and 40:20, with a mean age of 70.20 ± 6.09 and 68.20 ± 7.00 years, respectively.

Patient selection criteria

Inclusion criteria: All patients were diagnosed with EPL or EEC based on gastroscopy and pathological diagnosis and conformed to the surgical indications, with an expected survival period of over 3 months and complete clinical data available.

Exclusion criteria: Patients with comorbid cardiocerebrovascular diseases (hypertension, heart diseases, liver disorders, kidney diseases, *etc.*), autoimmune deficiency, coagulation dysfunction, cognitive impairment, or psychological disorders, such as depression, as well as those with other concurrent malignant tumors.

Methods

The control group received a conventional thoracotomy. The specific measures were as follows. After routine disinfection, an incision was created from the posterior–lateral part of the left chest, and the lateral muscle group and intercostal muscles were dissected. Subsequently, the nature, size, and location of the esophageal tumor were identified, and the lesion and enlarged lymph nodes were removed. An effective resection was performed at a position 6–8 cm above the tumor, and a gastric tube and a nutrition tube were placed. Finally, routine sutures and hemostasis were performed.

The research group underwent ESD. Magnifying endoscopy combined with image-enhanced technology was used to assess the microvascular and microsurface structures of the lesions, enabling precise pathological tissue identification. Part of the tissue was extracted through the gastroscope for biopsy, and iodine staining was conducted to assess whether it met the EC or EPL pathological criteria. The iodine staining patterns within the lesion areas were meticulously analyzed to clearly define the lesion boundaries. The distribution range and metastasis status of the lesion were then evaluated using endoscopic ultrasonography. An argon knife electrocoagulation was utilized to mark the area adjacent to the lesion, and a mixture consisting of glycerol fructose (to rapidly elevate the lesion and minimize the bleeding risk) and methylene blue (to enhance lesion visibility and delineate its margins) was injected into the lesion and the surrounding mucosa to make the lesion protrude. The injection volume was tailored based on the lesion's size and location, ranging from 5 to 10 mL. The mucosa adjacent to the lesion was then cut off with a needle-like knife along the mark, and the mucosal tissue at the lower edge of the lesion was gradually dissected to achieve complete resection. Anti-infection and hemostasis were performed postoperatively to prevent cross-infection.

Outcome measures

Efficacy evaluation: The dissection area and the resection rate per unit time (calculated as the dissection area-to-operation duration ratio) of patients in both groups were compared and recorded.

Complication assessment: Cases with adverse events, including delayed bleeding, wound infection, esophageal reflux, and postoperative esophageal stenosis in both groups, were observed and counted, with the incidence rate calculated.

Surgery-related parameter analysis: The bleeding volume, operation duration, and hospital length of stay of both groups were assessed and compared.

STM measurement: Preoperatively and 1 week postoperatively, 5 mL of early-morning venous blood was collected on an empty stomach and sent to the laboratory for assessment after centrifugation. Carcinoembryonic antigen (CEA), carbohydrate antigen 724 (CA724), and tumor-specific growth factor (TSGF) levels were determined using enzyme-linked immunosorbent assay.

Prognosis evaluation: All patients underwent a 6-month follow-up after discharge using telephone, QQ, WeChat, and email to record and statistically analyze their recurrence rates.

Statistical analysis

In this research, the Statistical Package for the Social Sciences version 21.0 statistical software was used for data analysis. Statistical description was conducted using mean ± SE of the mean for quantitative data. The comparison of quantitative data between the two groups was conducted using the *t*-test, and the paired *t*-test was utilized for the comparison between pre- and posttreatment data within the group. Frequency (percentage) was used for statistical description and the intergroup comparison was conducted using the χ^2 test for qualitative data. A P value of < 0.05 was considered statistically significant.

RESULTS

Comparative analysis of baseline data

No significant differences were observed in the baseline data, such as gender, age, disease course, lesion site, and family medical history, between the control and research groups ($P > 0.05$, Table 1).

Comparative analysis of therapeutic efficacy

The dissection area in the research group was statistically greater than in the control group ($P < 0.001$), as was the resection rate per unit time ($P < 0.001$, Table 2).

Comparative analysis of complications

Delayed bleeding, wound infection, esophageal reflux, and postoperative esophageal stenosis were observed in 3, 9, 19, and 9 cases in the control group and 2, 0, 4, and 4 cases in the research group, respectively. Incidences of wound infection, esophageal reflux, and total complications were markedly lower in the research group than in the control group ($P < 0.05$, Table 3).

Comparative analysis of surgery-related indexes

Statistical analysis of the bleeding volume, operation duration, and hospital length of stay of the two groups revealed that each indicator in the research group was significantly lower than that in the control group ($P < 0.001$, Table 4).

Comparative analysis of STMs

Analysis of STMs, including CEA, CA724, and TSGF, pre- and postoperatively revealed no significant between-group differences in all markers preoperatively ($P > 0.05$). Further, all markers in both groups exhibited a significant downward trend postoperatively ($P < 0.01$), with more notable decreases in the research group than in the control group ($P < 0.05$, Table 5).

Comparative analysis of 6-month postoperative recurrence

The control and research groups involved five and 2 recurrence cases, respectively, 6 months postoperatively. The two groups were not statistically different in the recurrence rate ($\chi^2 = 1.365$, $P = 0.243$, Figure 1).

DISCUSSION

This study revealed that both the dissection area and the resection rate per unit time were statistically higher in the research group than in the control group, indicating that ESD demonstrates superior efficacy compared to thoracotomy in treating patients with EPL or EEC. During the ESD procedure, surgeons introduce an endoscope into the esophagus and conduct precise manipulations to obtain high-quality tissue samples, thereby facilitating the acquisition of more accurate pathological assessment information. This, in turn, enables more appropriate treatment regimen formulation based on lesion severity[14]. The most prevalent complications in the control group include esophageal reflux, wound infection, postoperative esophageal stenosis, and delayed bleeding, whereas esophageal reflux, postoperative esophageal stenosis, and delayed bleeding were observed in the research group. The research group demonstrated a lower overall complication rate than the control group, indicating that ESD is associated with a higher safety profile in treating patients with EPL or EEC. Yu *et al*[15] revealed the operation duration as an independent predictor of postoperative esophageal stenosis in patients with EEC or EPL. In the current study, the shorter operation duration of ESD helps, to a certain extent, decrease the risk of postoperative esophageal stenosis. Furthermore, the research group demonstrated significant reductions in bleeding volume, operation duration, and hospital length of stay. This indicates that ESD for patients with EPL or EEC is beneficial for reducing intraoperative bleeding, shortening the surgical procedure, and facilitating recovery. The underlying mechanism may involve the introduction of normal saline or other injections into the esophageal submucosa *via* an endoscope during ESD surgery for the mucosal layer bulges to form a protrusion, enhancing surgical field clarity and lesion boundary demarcation, and consequently reducing bleeding and tissue damage[16]. Moreover, ESD only requires tissue sampling from the local lesion rather than complete esophageal resection, which obviates the requirement for total esophageal reconstruction surgery and promotes rapid patient recovery[17]. Li *et al*[18] revealed that preincision traction using an internal clip-with-spring device in colorectal ESD treatment, compared with conventional on-demand traction, further shortened the operation duration and postoperative hospital length of stay while being advantageous in reducing the amount of submucosal injection, the intraoperative bleeding rate, and the muscle injury rate . The application of this technique in esophageal ESD treatment may yield similar improvement effects, which needs comparative analysis in future research. CEA is intimately associated with EC occurrence, and both CEA and CA724 exert a strong connection with bone metastases in EC. Further, TSGF is significantly correlated with pathological progression, such as the tumor location, lymph node involvement, and TNM staging of EC, as well as prognosis[19-21]. Hence, this study analyzed the effect of ESD on the indices in patients with EPL or EEC. Our data revealed an evident decline in CEA, CA724, and TSGF levels in the research group postoperatively, which were lower compared with the baseline and those of the control group. This indicates that ESD significantly downregulates the abnormally increased serum STM levels in patients with EPL or EEC.

Table 1 Comparative analysis of baseline data

Indicators	Control group (*n* = 60)	Research group (*n* = 60)	*t* value	*P* value
Gender, *n* (%)			0.352	0.553
Male	43 (71.67)	40 (66.67)		
Female	17 (28.33)	20 (33.33)		
Age (years)	70.20 ± 6.09	68.20 ± 7.00	1.670	0.098
Disease course (years)	2.70 ± 0.67	2.58 ± 0.67	0.981	0.329
Lesion site, *n* (%)			0.357	0.836
Upper esophageal segment	20 (33.33)	23 (38.33)		
Middle esophageal segment	23 (38.33)	22 (36.67)		
Lower esophageal segment	17 (28.33)	15 (25.00)		
Family medical history, *n* (%)			0.745	0.388
Without	48 (80.00)	44 (73.33)		
With	12 (20.00)	16 (26.67)		

Table 2 Comparative analysis of therapeutic efficacy

Indicators	Control group (*n* = 60)	Research group (*n* = 60)	*t* value	*P* value
Dissection area (cm^2)	6.76 ± 5.95	10.17 ± 4.64	3.501	< 0.001
Resection rate per unit time (mm^2/min)	3.03 ± 3.20	9.65 ± 6.54	7.043	< 0.001

Table 3 Comparative analysis of complications, *n* (%)

Indicators	Control group (*n* = 60)	Research group (*n* = 60)	χ^2 value	*P* value
Delayed bleeding	3 (5.00)	2 (3.33)	0.209	0.648
Wound infection	9 (15.00)	0 (0.00)	9.730	0.002
Esophageal reflux	19 (31.67)	4 (6.67)	12.102	< 0.001
Postoperative esophageal stenosis	9 (15.00)	4 (6.67)	2.157	0.142
Total	40 (66.67)	10 (16.67)	30.857	< 0.001

Table 4 Comparative analysis of surgery-related indexes

Indicators	Control group (*n* = 60)	Research group (*n* = 60)	*t* value	*P* value
Bleeding volume (mL)	151.83 ± 126.35	31.75 ± 23.68	7.236	< 0.001
Operation duration (hours)	4.05 ± 1.14	2.15 ± 1.02	9.621	< 0.001
Hospital length of stay (days)	21.70 ± 6.52	9.63 ± 2.31	13.516	< 0.001

Considering the occult symptoms of EEC, patients are more likely to be diagnosed in the middle and late stages, causing not only a high risk of posttreatment recurrence but also a relatively low 5-year survival rate[22]. Therefore, this study also analyzed the effect of ESD on the recurrence rate of patients. A 6-month follow-up indicated a comparable recurrence rate in the research group (3.33%) compared to the control group, indicating that ESD will not increase the recurrence risk in patients with EPL or EEC. Wu *et al*[23] applied ESD to patients with EPL or EEC and achieved a surgical success rate of 96.6%. This indicates a certain safety and reliability level of the ESD procedure, along with low recurrence and complication rates. Ling *et al*[24], which enrolled 89 cases of EPL and EEC treated with ESD, reported one recurrence case. Additionally, Xu *et al*[25] demonstrated that ESD has a low incidence of residual lesions and recurrence in elderly patients with early gastric cancer and precancerous lesions and is beneficial for promoting gastric cell and glandular function recovery, which supports our research results. Besides the above-mentioned treatment modalities, several investigators have conducted relevant studies on the treatment approaches for EPL and EEC. For instance, Zheng

Table 5 Comparative analysis of serum tumor markers

Indicators	Control group (*n* = 60)	Research group (*n* = 60)	*t* value	*P* value
CEA (ng/mL)				
Before surgery	12.65 ± 3.33	12.86 ± 3.66	0.329	0.743
After surgery	3.19 ± 2.15[a]	2.35 ± 1.60[a]	2.428	0.017
CA724 (U/mL)				
Before surgery	27.53 ± 5.35	28.27 ± 5.40	0.754	0.452
After surgery	4.06 ± 3.70[a]	2.77 ± 1.93[a]	2.394	0.018
TSGF (U/mL)				
Before surgery	96.50 ± 20.80	97.37 ± 22.00	0.223	0.824
After surgery	49.83 ± 13.26[a]	39.22 ± 14.18[a]	4.233	< 0.001

[a]$P < 0.05$ *vs* the preoperative level.

CEA: Carcinoembryonic antigen; CA724: Carbohydrate antigen 724; TSGF: Tumor-specific growth factor.

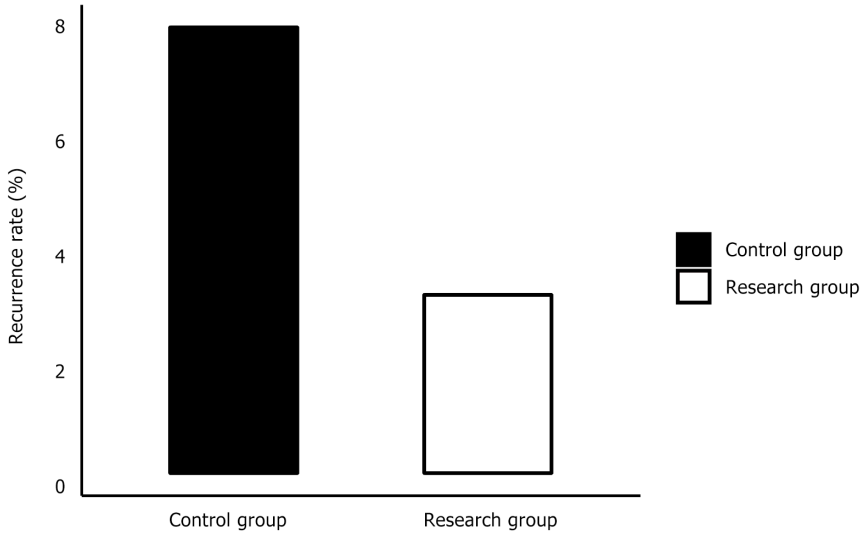


Figure 1 Comparative analysis of the 6-month postoperative recurrence rates between the control group (*n* = 60; 5 recurrence cases) and the research group (*n* = 60; 2 recurrence cases; 8.33% *vs* 3.33%). Intergroup comparison was performed using the χ^2 test.

et al[26] have demonstrated that both multi-band mucosectomy (MBM) and ESD can be effectively utilized in treating patients with EPL or EEC. MBM presents the advantages of shorter hospitalization duration, faster recovery, and lower cost, whereas ESD offers benefits such as a high complete resection rate of the lesions, the ability to avoid positive resection margins, and the reduction of the risks associated with secondary treatments and additional surgeries. Furthermore, Xie *et al*[27] demonstrated that clip traction helps in esophageal ESD treatment by increasing the operative field exposure, which is conducive to reducing the risk of injury to the muscularis propria and shortening the dissection time. Further, evidence revealed that cryotherapy can be used to treat patients with EPL, which induces refrigerants (liquid nitrogen or carbon dioxide) to destroy tumor tissues through rapid cooling and thawing cycles, thereby playing a therapeutic role[28].

This study has several limitations to be improved. First, long-term follow-up could be incorporated to analyze the extended effect of ESD treatment on patients' quality of life, which would provide deeper information into the potential clinical value of ESD. Second, expanding the analysis to include factors that affect treatment efficacy, complications, and prognosis in patients with EPL or EEC post-ESD would help determine crucial determinants, thereby facilitating the development of more targeted clinical optimization strategies. Third, coordinating multicenter efforts to obtain large-sample data for prospective studies would further improve the accuracy and generalizability of the research findings. Future research will focus on these directions to maximize the study's clinical applicability and practical significance.

CONCLUSION

In conclusion, ESD application in patients with EPL or EEC significantly improved the dissection area and the resection rate per unit time while reducing the risk of complications, including delayed bleeding, wound infection, esophageal reflux, and postoperative esophageal stenosis. Moreover, it reduced intraoperative bleeding, shortened operation duration and hospital stays, facilitated recovery, and suppressed the abnormal levels of serum CEA, CA724, and TSGF.

FOOTNOTES

Author contributions: Yuan XC designed the research and wrote the first manuscript; Yuan XC, Jia P, Tian T, Zhu J and Zhang XY contributed to conceiving the research and analyzing data; Yuan XC conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

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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

Magnetic resonance imaging bias field correction improves tumor prognostic evaluation after transcatheter arterial chemoembolization for liver cancer

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Abstract

BACKGROUND

Transcatheter arterial chemoembolization (TACE) is a key treatment approach for advanced invasive liver cancer (infiltrative hepatocellular carcinoma). However, its therapeutic response can be difficult to evaluate accurately using conventional two-dimensional imaging criteria due to the tumor's diffuse and multifocal growth pattern. Volumetric imaging, especially enhanced tumor volume (ETV), offers a more comprehensive assessment. Nonetheless, bias field inhomogeneity in magnetic resonance imaging (MRI) poses challenges, potentially skewing volumetric measurements and undermining prognostic evaluation.

AIM

To investigate whether MRI bias field correction enhances the accuracy of volumetric assessment of infiltrative hepatocellular carcinoma treated with TACE, and to analyze how this improved measurement impacts prognostic prediction.

METHODS

We retrospectively collected data from 105 patients with invasive liver cancer who underwent TACE treatment at the Affiliated Hospital of Xuzhou Medical University from January 2020 to January 2024. The improved N4 bias field correction algorithm was applied to process MRI images, and the ETV before and after treatment was calculated. The ETV measurements before and after correction were compared, and their relationship with patient prognosis was analyzed. A Cox proportional hazards model was used to evaluate prognostic factors, with Martingale residual analysis determining the optimal cutoff value, followed by survival analysis.

RESULTS

Bias field correction significantly affected ETV measurements, with the corrected baseline ETV mean (505.235 cm^3) being significantly lower than before correction (825.632 cm^3, $P < 0.001$). Cox analysis showed that the hazard ratio (HR) for corrected baseline ETV (HR = 1.165, 95%CI: 1.069-1.268) was higher than before correction (HR = 1.063, 95%CI: 1.031-1.095). Using 412 cm^3 as the cutoff, the group with baseline ETV < 415 cm^3 had a longer median survival time compared to the ≥ 415 cm^3 group (18.523 months *vs* 8.926 months, $P < 0.001$). The group with an ETV reduction rate ≥ 41% had better prognosis than the < 41% group (17.862 months *vs* 9.235 months, $P = 0.006$). Multivariate analysis confirmed that ETV reduction rate (HR = 0.412, $P < 0.001$), Child-Pugh classification (HR = 0.298, $P < 0.001$), and Barcelona Clinic Liver Cancer stage (HR = 0.578, $P = 0.045$) were independent prognostic factors.

CONCLUSION

Volume imaging based on MRI bias field correction can improve the accuracy of evaluating the efficacy of TACE treatment for invasive liver cancer. The corrected ETV and its reduction rate can serve as independent indicators for predicting patient prognosis, providing important reference for developing individualized treatment strategies.

Key Words: Invasive liver cancer; Transcatheter arterial chemoembolization; Magnetic resonance imaging; Bias field correction; Volume imaging

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Core Tip: This study highlights the value of magnetic resonance imaging bias field correction in improving enhanced tumor volume measurements for evaluating transcatheter arterial chemoembolization efficacy in invasive liver cancer. Corrected enhanced tumor volume and its reduction rate were identified as independent prognostic factors, enhancing accuracy in assessing tumor burden and outcomes. These findings support integrating bias field correction into imaging protocols to optimize treatment strategies and improve prognostic evaluations in interventional oncology.

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INTRODUCTION

Infiltrative hepatocellular carcinoma (iHCC) is a distinctive type of primary liver cancer characterized by diffuse infiltrative growth, unclear boundaries, and diagnostic challenges[1]. Compared to nodular hepatocellular carcinoma, iHCC has a poorer prognosis and significantly shorter median survival[2]. Transcatheter arterial chemoembolization (TACE) is a crucial treatment for advanced iHCC, but accurately assessing treatment efficacy is challenging due to the tumor's infiltrative nature[3].

Traditional criteria for evaluating solid tumor response, such as the World Health Organization criteria and the Modified Response Evaluation Criteria in Solid Tumors, primarily rely on changes in the maximum tumor diameter[4]. However, these standards have limitations in assessing iHCC. The tumor's unclear boundaries and multifocal fusion make it difficult to measure the maximum diameter accurately, and two-dimensional measurements cannot fully capture the spatial distribution and overall tumor burden[5]. Recently, advancements in volumetric imaging have provided new approaches to overcoming these challenges[6]. Magnetic resonance imaging (MRI), with its high soft tissue resolution and multiparametric imaging capabilities, plays a significant role in evaluating iHCC treatment response. However, MRI images are susceptible to bias field inhomogeneity, potentially leading to signal intensity anomalies and volumetric measurement errors[7].

Bias field correction is a crucial technique for improving MRI image quality. By compensating for factors like radiofrequency coil sensitivity and static field inhomogeneity, it achieves more accurate signal intensity distribution[8]. Nonetheless, research on the application of bias field correction in iHCC volumetric measurement is limited, and its impact on TACE efficacy evaluation has not been systematically validated. Enhanced tumor volume (ETV), a novel quantitative assessment metric that considers both tumor volume and enhancement characteristics, may provide a more objective basis for evaluating iHCC treatment response[9]. However, the accuracy of ETV measurement largely depends on image quality, and bias field inhomogeneity may affect its prognostic value[10].

Therefore, this study aims to explore the application value of volumetric imaging based on MRI bias field correction in assessing the efficacy of TACE treatment for iHCC. By comparing ETV measurements before and after correction, we analyze their relationship with patient prognosis, providing new technical methods and clinical evidence to enhance the accuracy of iHCC treatment response evaluation. This has significant clinical implications for optimizing individualized

treatment strategies and improving patient outcomes. Additionally, this study will serve as a reference for establishing a more scientific efficacy evaluation system for iHCC.

MATERIALS AND METHODS

A retrospective collection of patients diagnosed with primary iHCC and treated with TACE surgery from January 2020 to January 2024 at our hospital was conducted. The study included a total of 150 patients, with a mean age of 58.7 ± 10.4 years (range: 35-78 years). The majority of patients were male (72.0%, n = 108), reflecting the higher prevalence of liver cancer in males.

Criteria

Inclusion criteria: (1) Age between 18-70 years; (2) Confirmed by pathological biopsy or imaging examinations (meeting the following characteristics: Significant hyposignal on T1-weighted images, homogeneous light to moderate high signal on T2-weighted images; (3) Significant pseudo-capsule enhancement in the arterial phase, and significant contrast agent washout in the delayed phase) consistent with the diagnosis of iHCC[11]; (4) Eastern Cooperative Oncology Group performance status ≤ 3[12]; (5) Child-Pugh classification A or B; (6) Barcelona Clinic Liver Cancer (BCLC) staging B, C, or D[13]; (7) Expected survival > 3 months; (8) Complete clinical data and follow-up information; and (9) Informed consent obtained and informed consent form signed.

Exclusion criteria: (1) Concurrent other malignant tumors; (2) Severe cardiac, pulmonary, or renal insufficiency; (3) Severe coagulation abnormalities (prothrombin time > 18 seconds or platelet count < 50 × 10^9/L); (4) Severe hepatic or renal damage (total bilirubin > 51.3 μmol/L); (5) Pregnant or lactating women; (6) Allergy to iodinated contrast media; (7) Contraindications for MRI examination (such as cardiac pacemaker, metallic implants, *etc.*); and (8) Inability to tolerate TACE surgery or presence of surgical contraindications.

TACE surgical treatment

All patients underwent TACE treatment under the guidance of Digital Subtraction Angiography. Preoperative laboratory tests were conducted, including complete blood count, coagulation function, liver and kidney function, and tumor markers. The surgery was performed under local anesthesia, using the modified Seldinger technique through puncture of the right femoral artery. First, celiac trunk, common hepatic artery, and superior mesenteric artery angiography were performed to comprehensively assess the arterial blood supply of the liver, tumor vascular characteristics, and the presence of abnormal feeding arteries. Based on the vascular anatomy, selective catheterization to the proper hepatic artery or left/right hepatic artery was performed, followed by super-selective catheterization to the tumor-feeding artery. For the conventional lipiodol TACE group (69 cases), lipiodol was emulsified with idarubicin (dose 10 mg) and lobaplatin (dose 30-50 mg) and slowly injected until significant reduction in tumor-feeding artery blood flow. For the drug-eluting bead group (36 cases), CalliSpheres® drug-loaded microspheres were used (Jiangsu Hengrui Medicine Co., Ltd.), mixing 100-300 μm or 300-500 μm microspheres with epirubicin (dose 50-75 mg), diluted with non-ionic contrast medium, and slowly transfused (Figure 1). Intraoperatively, special attention was paid to prevent non-target embolization, and angiography was closely monitored to avoid reflux. For patients with extrahepatic feeding arteries, additional embolization treatment was required after the main feeding artery was embolized. Postoperative angiography confirmed the embolization effect of the tumor-feeding artery and checked for non-target embolization. All patients received routine anti-infection, hepatoprotective, and symptomatic support treatment. Patients underwent liver function re-examination 2-3 days after surgery to assess for severe liver damage. Based on the patient's specific condition and willingness, imaging assessment was conducted 4-6 weeks later, and a second TACE treatment was performed if necessary. For patients undergoing multiple TACE treatments, the specific plan for each procedure (including embolization dosage, range, and timing) was individually adjusted based on the patient's general condition, liver function reserve, previous treatment response, and tumor progression. The following points should be noted during treatment: (1) For patients with portal vein invasion, the benefits and risks should be weighed, and a more conservative embolization strategy may be considered; (2) For patients with multiple lesions, treatment can be chosen based on tumor size and location; and (3) For patients with poor liver function reserve, the dose of chemotherapy drugs should be appropriately reduced, and the range of embolization should be decreased. All surgical operations were performed by physicians with more than 10 years of interventional treatment experience to ensure the safety and effectiveness of the surgery. The endpoints of treatment include the following situations: (1) Tumor progression or new lesions; (2) Significant deterioration of liver function; (3) Occurrence of severe complications; and (4) Patient refusal to continue treatment. All surgical complications were assessed and recorded according to the standards of the Society of Interventional Radiology.

MRI scanning protocol and image acquisition

All patients were examined using 1.5T or 3.0T MRI scanners (Magnetom Avanto or Skyra, Siemens Healthcare Systems, Germany). Standardized scanning sequences included: Transverse T1-weighted dual echo sequence (TR/TE1/TE2 = 200/2.2/4.4 milliseconds, matrix 256 × 192, slice thickness 5 mm, interslice gap 1 mm), respiratory-triggered T2-weighted fast spin echo sequence (TR/TE = 4500/84 milliseconds, matrix 320 × 240, slice thickness 5 mm, interslice gap 1 mm), diffusion-weighted imaging sequence (TR/TE = 7500/65 milliseconds, b-values = 0, 500, 800 seconds/mm², matrix 128 × 128, slice thickness 5 mm, interslice gap 1 mm). Dynamic contrast-enhanced scans were performed using the volumetric interpolated breath-hold examination sequence (TR/TE = 4.4/2.2 milliseconds, matrix 256 × 192, slice thickness 3 mm, no

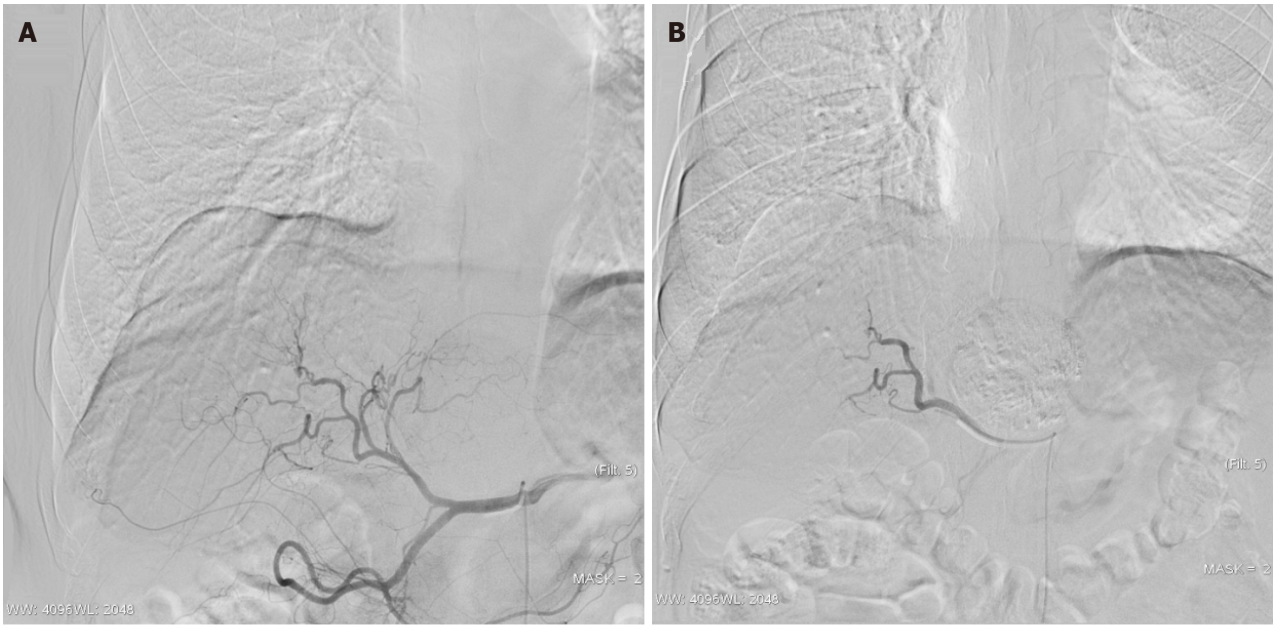


Figure 1 Angiographic images before and after transcatheter arterial chemoembolization procedure. A: The pre-transcatheter arterial chemoembolization image reveals a hypervascular tumor blush, indicating the presence of a highly vascularized liver tumor; B: The post-transcatheter arterial chemoembolization image demonstrates that the tumor blush has significantly decreased in intensity.

gap). Contrast agents used were gadopentetate dimeglumine (Magnevist, Bayer Healthcare) or gadobutrol (Gadovist, Bayer Healthcare), with a dose of 0.1 mmol/kg, injected *via* the antecubital vein at a rate of 3 mL/s, followed by a 20 mL saline flush. Fluorescence-triggered multi-phase dynamic contrast-enhanced scans were performed, including arterial phase (20-35 seconds after contrast injection), portal venous phase (60-75 seconds), delayed phase (180 seconds), and hepatobiliary phase (20 minutes). To ensure image quality, all scans were completed during breath-hold, with each breath-hold time controlled within 20 seconds. The scan range included the entire liver, and the field of view was adjusted to 350-400 mm according to the patient's body size.

Image registration and bias field correction

All patient MRI images were registered using a deformable field-based non-rigid registration algorithm. Initially, T1-weighted sequence images before and after TACE treatment were imported into a medical image processing workstation (Syngo.via VB20A, Siemens Healthcare Systems). The registration processed a multi-resolution strategy, optimizing from low resolution to the original resolution to improve registration efficiency and accuracy. The registration algorithm included two stages: Global affine transformation and local non-rigid deformation. In the global affine transformation stage, overall rotation, translation, and scaling parameters were determined by minimizing mutual information. In the local non-rigid deformation stage, a B-spline free-form deformation model and gradient-based similarity metric were used to fine-tune local deformations. To ensure registration quality, control points were set at a distance of 5 mm, with a deformation regularization parameter $\lambda = 0.01$ and a maximum of 200 iterations. Registration results were assessed by two radiologists with over 5 years of experience using a 5-point scale (1 point - very poor, 5 points - very good), and cases with scores below 3 required re-registration. Additionally, the quality of registration was quantitatively evaluated by calculating the normalized cross-correlation coefficient and structural similarity index of the images before and after registration, with requirements of normalized cross-correlation coefficient > 0.85 and structural similarity index > 0.80. The resulting deformation fields were used to establish spatial correspondence between different sequences and phases in subsequent analyses.

This study employed a semi-automatic segmentation method combining deep learning with manual correction for three-dimensional segmentation of the liver and tumors. Initially, a deep convolutional neural network based on the 3D U-Net architecture was used for rough segmentation of the liver, with an encoder-decoder structure, including 4 down-sampling and 4 up-sampling layers, each using two 3 × 3 × 3 convolutional kernels and ReLU activation functions. To improve segmentation accuracy, data augmentation techniques were used during the training phase, including random rotation (± 15°), scaling (0.8-1.2), and elastic deformation. The network training used a combined loss function, including Dice loss and weighted cross-entropy loss, with a weight ratio of 1:1. After obtaining preliminary segmentation results, manual corrections were made by two radiologists with over 8 years of experience using three-dimensional segmentation software (Syngo.via MM Oncology, Siemens Healthcare Systems). The segmentation process was synchronized in the axial, sagittal, and coronal directions to ensure continuity and accuracy. For tumor regions, based on multi-phase contrast-enhanced scan features, a semi-automatic watershed algorithm was used for preliminary segmentation on arterial phase images, combined with portal venous and delayed phase image features for boundary optimization. Segmentation results were quality-controlled by calculating the Dice coefficient and volume overlap rate, requiring a Dice coefficient > 0.90 and a volume overlap rate > 0.85. The final segmentation results were used for subsequent quantitative

analysis and evaluation.

To eliminate bias field inhomogeneity in MRI images, this study employed an improved N4 bias field correction algorithm for whole-liver volume correction. The algorithm is based on the N4 Intensity Transformation Kit framework, approximating the bias field distribution with B-spline basis functions. The correction process first applies a logarithmic transformation to the input image, converting multiplicative bias fields to additive bias fields. Subsequently, a multi-scale iterative strategy is used to estimate the bias field at different resolution levels. Each scale level is set with a maximum of 50 iterations, a convergence threshold of 0.001, and an initial B-spline control point distance of 30 mm, gradually reduced to 10 mm during iteration. To improve the correction effect, a tissue segmentation-based constraint term is introduced, using the aforementioned liver segmentation results as a mask to correct only the liver region. The correction process uses the Otsu thresholding method to adaptively estimate different tissue categories, optimizing bias field estimation by minimizing intra-class variance. The correction effect is evaluated by calculating the coefficient of variation of the image intensity, requiring a reduction of over 30% in the coefficient of variation value of the liver parenchymal region after correction. Additionally, the correction effect is verified by comparing the uniformity of the gray-level histogram and the signal intensity profile before and after correction. The final correction results were used for subsequent quantitative feature extraction and analysis.

ETV measurement and assessment methods

This study used enhanced volume as the main quantitative assessment indicator. Based on the aforementioned segmentation results and bias field-corrected images, a voxel-based analysis method was used for tumor volume calculation. Initially, on arterial phase images, the region of interest (ROI) was determined according to World Health Organization standards to include all visible tumor tissue. By comparing with portal venous and delayed phase images and combining tumor enhancement features, the ROI boundary was further optimized to exclude necrotic areas and non-tumor tissue. Tumor volume was calculated using three-dimensional reconstruction software (Syngo.via VB20A, Siemens Healthcare Systems) by accumulating voxels within the ROI on each axial slice and correcting the volume considering slice thickness and interslice gap. To ensure measurement accuracy, measurements were made by two radiologists with over 8 years of experience, and their average values were taken as the final results. Inter-measurer consistency was assessed using the Intraclass Correlation Coefficient, requiring an Intraclass Correlation Coefficient > 0.85. For the evaluation of TACE treatment effects, the absolute change in ETV before and after treatment (ΔETV = post-treatment ETV - pre-treatment ETV) and the relative change percentage (ETV% = ΔETV/pre-treatment ETV × 100%) were calculated. Additionally, to verify the impact of MRI bias field correction on measurement results, the aforementioned measurements were performed on both original and bias field-corrected images and compared. In patients with multiple lesions, the maximum lesion method was used, *i.e.*, the lesion with the largest diameter was selected for measurement and follow-up assessment. Furthermore, for cases with portal vein invasion, the tumor thrombus in the portal vein was included in the measurement range. To reduce the impact of partial volume effects, for lesions with blurred edges, a semi-automatic threshold segmentation method was used, combined with morphological operations for boundary optimization.

Statistical analysis

The study employed a rigorous set of statistical analysis methods. First, the data was processed and analyzed using SPSS 26.0 software and R software version 4.1.0. Continuous variables with normal distribution were represented as mean ± SD, and paired *t*-tests were used to compare differences in ETV before and after TACE treatment. Non-normally distributed variables were represented as median (interquartile range), and the Wilcoxon rank-sum test was used for group comparisons. Categorical variables were represented as number (percentage) and analyzed using χ^2 tests or Fisher's exact tests. For survival analysis, the study used the Kaplan-Meier method to plot survival curves and the log-rank test for group comparisons. Additionally, the Cox proportional hazards regression model was applied to analyze risk factors affecting patient survival, calculating the hazard ratio (HR) and its 95% confidence interval (CI). To evaluate the non-linear relationships between continuous variables and prognosis, the study employed the local weighted scatterplot smoothing (LOWESS) method and the Q statistic method maximizing the standardized log-rank statistic.

RESULTS

Baseline characteristics analysis of the study subjects

A total of 105 patients with iHCC were included in this study, consisting of 78 males (74.29%) and 27 females (25.71%). In terms of age distribution, 74 patients (70.48%) were under 65 years old, and 31 patients (29.52%) were 65 years old or above. In etiological analysis, hepatitis B virus infection was the most common, accounting for 89 cases (84.76%), followed by hepatitis C virus infection with 9 cases (8.57%), alcoholic liver disease with 7 cases (6.66%), and cryptogenic liver cancer with 1 case (0.95%). A total of 71 patients (67.62%) had concurrent liver cirrhosis.

Regarding disease staging and scoring, according to the BCLC, there were 31 patients (29.52%) in stage B, 71 patients (67.62%) in stage C, and 3 patients (2.86%) in stage D. In the Child-Pugh classification, there were 70 patients (66.67%) in grade A, 34 patients (32.38%) in grade B, and 1 patient (0.95%) in grade C. Eastern Cooperative Oncology Group performance status showed that 58 patients (55.24%) had a score of 0, 41 patients (39.05%) had a score of 1, 4 patients (3.81%) had a score of 2, and 2 patients (1.90%) had a score of 3. Analysis of tumor characteristics revealed that 19 patients (18.10%) had a single lesion, 20 patients (19.05%) had 2 Lesions, 12 patients (11.43%) had 3 Lesions, and 54 patients (51.43%) had 4 or more lesions. The average maximum tumor diameter was 8.72 cm (range 1.6-19.8 cm), with a median of 8.15 cm (interquartile range 5.2-11.8 cm). Portal vein invasion was present in 44 patients (41.90%), and extrahepatic

metastasis occurred in 9 patients (8.57%).

In terms of treatment regimens, 69 patients (65.71%) underwent conventional lipiodol TACE, and 36 patients (34.29%) received drug-eluting bead treatment. The distribution of treatment sessions was as follows: 50 patients (47.62%) had a single treatment, 19 patients (18.10%) had two treatments, 14 patients (13.33%) had three treatments, and 22 patients (20.95%) had four or more treatments. During the follow-up period, 81 patients (77.14%) died, and 24 patients (22.86%) were alive. The average follow-up time was 17.32 months (range 0.21-142.55 months), with a median follow-up time of 10.95 months (interquartile range 4.23-21.32 months) (Table 1).

The impact of MRI bias field correction on ETV measurement and prognostic prediction

Comparative analysis showed (Table 2), MRI bias field correction significantly affected the measurement results of tumor volume before and after TACE treatment. At baseline, the mean ETV without bias field correction was 825.632 cm^3 (range: 63.523-3563.126 cm^3), while the mean ETV after bias field correction dropped to 505.235 cm^3 (range: 142.352-1292.223 cm^3), with a statistically significant difference between the two groups ($P < 0.001$). Similarly, after TACE treatment, the mean ETV without bias field correction was 632.523 cm^3 (range: 47.235-3382.532 cm^3), and it dropped to 325.236 cm^3 (range: 110.135-1018.516 cm^3) after bias field correction, with a statistically significant difference ($P < 0.001$).

Cox proportional hazards model analysis indicated (Table 3), in measurements not using bias field correction, the HR for baseline ETV was 1.063 (95%CI: 1.031-1.095, $P < 0.001$), while the HR for baseline ETV using bias field correction increased to 1.165 (95%CI: 1.069-1.268, $P < 0.001$). For absolute ETV change, the HR for the uncorrected group was 1.012 (95%CI: 0.985-1.042, $P = 0.481$), and for the corrected group, it was 1.040 (95%CI: 0.935-1.160, $P = 0.512$), with neither group showing statistical significance. However, for the percentage change in ETV, the HR for the uncorrected group was 1.005 (95%CI: 0.981-1.030, $P = 0.793$), and it significantly decreased to 0.665 (95%CI: 0.538-0.825, $P < 0.001$) for the corrected group.

Analysis using Martingale residual LOWESS smoothing curves (Figure 2A) showed a clear turning point in the curve of ETV before the first TACE treatment, indicating that the critical value using the Cox model is appropriate as an indicator variable for baseline ETV. According to the Q statistic method (Figure 2B), the critical value for baseline ETV using bias field correction was determined to be 412 cm^3 ($P = 0.003$). Similarly, for the analysis of the percentage change in ETV (Figure 3A), the Martingale residual LOWESS smoothing curve showed a trend of decreasing and then increasing, suggesting that using the reduction rate of ETV before and after treatment as a linear variable in the Cox model may not be suitable and should be transformed into an indicator with an appropriate critical value. After Q statistic analysis (Figure 3B), the critical value for the percentage change in ETV before and after TACE treatment using magnetic resonance bias field correction was determined to be 40.253% ($P = 0.010$).

Survival analysis based on ETV thresholds and prognostic factor assessment

Based on the analysis results of the critical values, we grouped patients and assessed their survival status. In the pre-treatment ETV threshold grouping, 45 patients (42.86%) had ETV < 415 cm^3, and 60 patients (57.14%) had ETV ≥ 415 cm^3. Kaplan-Meier survival analysis showed that the median survival time for patients with ETV < 415 cm^3 was 18.523 months (95%CI: 14.862-29.635 months), while for patients with ETV ≥ 415 cm^3, the median survival time was 8.926 months (95%CI: 5.923-10.832 months). The quartile analysis revealed that the 25th, 50th, and 75th survival time points for the ETV < 415 cm^3 group were 10.523 months (95%CI: 4.862-15.235 months), 18.523 months (95%CI: 14.862-29.635 months), and 35.862 months (95%CI: 22.523-45.236 months), respectively; for the ETV ≥ 415 cm^3 group, the corresponding time points were 3.862 months (95%CI: 1.523-5.862 months), 8.926 months (95%CI: 5.923-10.832 months), and 15.235 months (95%CI: 10.523-19.862 months). The comparison of survival curves between the two groups showed a statistically significant difference (log-rank test, $P < 0.001$) (Table 4).

In the ETV reduction rate threshold grouping before and after treatment, 58 patients (55.24%) had an ETV reduction rate < 41%, and 47 patients (44.76%) had an ETV reduction rate ≥ 41%. The median survival time for patients with an ETV reduction rate < 41% was 9.235 months (95%CI: 5.862-12.523 months), while for patients with an ETV reduction rate ≥ 41%, the median survival time was 17.862 months (95%CI: 13.926-20.635 months). The quartile analysis showed that the 25th, 50th, and 75th survival time points for the ETV reduction rate < 41% group were 3.235 months (95%CI: 1.523-5.862 months), 9.235 months (95%CI: 5.862-12.523 months), and 15.235 months (95%CI: 10.235-31.523 months), respectively; for the ETV reduction rate ≥ 41% group, the corresponding time points were 10.523 months (95%CI: 6.523-14.862 months), 17.862 months (95%CI: 13.926-20.635 months), and 29.635 months (95%CI: 19.862-72.523 months). The comparison of survival curves between the two groups showed a statistically significant difference (log-rank test, $P = 0.006$) (Table 5).

Univariate and multivariate analysis of prognostic factors

To comprehensively assess the factors affecting patient prognosis, this study conducted univariate and multivariate Cox regression analyses on baseline ETV and the rate of ETV reduction. In the analysis of baseline ETV (Table 6), univariate analysis showed that the following factors were significantly associated with patient prognosis: Pre-treatment ETV (≥ 415 cm^3 *vs* < 415 cm^3, HR = 1.982, 95%CI: 1.212-3.236, $P = 0.012$), Child-Pugh classification (Class A *vs* class B or C, HR = 0.423, 95%CI: 0.252-0.668, $P < 0.001$), and BCLC staging (Stage B *vs* stage C or D, HR = 0.523, 95%CI: 0.318-0.852, $P = 0.013$). The results of the multivariate analysis indicated that Child-Pugh classification (HR = 0.432, 95%CI: 0.256-0.702, $P < 0.001$) and BCLC staging (HR = 0.538, 95%CI: 0.318-0.916, $P = 0.023$) remained independent prognostic factors. Notably, age (per one-year increase, HR = 1.008, 95%CI: 0.964-1.032, $P = 0.832$), gender (female *vs* male, HR = 0.728, 95%CI: 0.416-1.282, $P = 0.273$), and type of TACE (lipiodol *vs* drug-eluting bead-TACE, HR = 1.016, 95%CI: 0.612-1.682, $P = 0.976$) did not show statistical significance in the multivariate analysis.

Table 1 Analysis of general patient information, *n* (%)

Item	Statistic
Total number of patients, baseline	105
Age	
< 65 years old	74 (70.48)
≥ 65 years old	31 (29.52)
Gender	
Male	78 (74.29)
Female	27 (25.71)
Survival status at analysis	
Alive	24 (22.86)
Deceased	81 (77.14)
Follow-up time (months)	
Mean (range)	17.32 (0.21-142.55)
Median (interquartile range)	10.95 (4.23-21.32)
Etiology	
Hepatitis B virus	89 (84.76)
Hepatitis C virus	9 (8.57)
Alcoholic liver disease	7 (6.66)
Cryptogenic liver cancer	1(0.95)
Cirrhosis	71 (67.62)
Barcelona Clinic Liver Cancer staging	
B	31 (29.52)
C	71 (67.62)
D	3 (2.86)
Child-Pugh classification	
A	70 (66.67)
B	34 (32.38)
C	1 (0.95)
ECOG performance status	
0	58 (55.24)
1	41 (39.05)
2	4 (3.81)
3	2 (1.90)
Number of tumors	
1	19 (18.10)
2	20 (19.05)
3	12 (11.43)
More than 4	54 (51.43)
Tumor size (cm)	
Mean (range)	8.72 (1.6-19.8)
Median (interquartile range)	8.15 (5.2-11.8)
Portal vein invasion	

Yes	44 (41.90)
No	61 (58.10)
Extrahepatic metastasis	
Yes	9 (8.57)
No	96 (91.43)
TACE Type	
Lipiodol	69 (65.71)
Drug-eluting beads	36 (34.29)
Number of TACE treatments	
1	50 (47.62)
2	19 (18.10)
3	14 (13.33)
4 or more than 4	22 (20.95)

ECOG: Eastern Cooperative Oncology Group; TACE: Transcatheter arterial chemoembolization.

Table 2 Comparison of effective tumor volume before and after transcatheter arterial chemoembolization treatment with and without magnetic resonance bias field correction

Variables baseline ETV	Mean (interval) (cm^3)		*P* value
	No MR bias field correction	With MR bias field correction	
After TACE treatment	825.632 (63.523-3563.126)	505.235 (142.352-1292.223)	< 0.001
ETV	632.523 (47.235-3382.532)	325.236 (110.135-1018.516)	< 0.001

ETV: Effective tumor volume; TACE: Transcatheter arterial chemoembolization; MR: Magnetic resonance.

Table 3 Hazard ratios of baseline effective tumor volume, absolute effective tumor volume change, and effective tumor volume% with and without magnetic resonance bias field correction

Variable	Not using bias field correction		Use bias field correction	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Baseline ETV	1.063 (1.031-1.095)	< 0.001	1.165 (1.069-1.268)	< 0.001
Absolute ETV change	1.012 (0.985-1.042)	0.481	1.040 (0.935-1.160)	0.512
ETV%	1.005 (0.981-1.030)	0.793	0.665 (0.538-0.825)	< 0.001

ETV: Effective tumor volume.

Table 4 Survival time of different effective tumor volume groups before transcatheter arterial chemoembolization treatment

Percentage (%)	< 415 cm^3		≥ 415 cm^3	
	Survival time (months)	95%CI	Survival time (months)	95%CI
25	10.523	4.862-15.235	3.862	1.523-5.862
50	18.523	14.862-29.635	8.926	5.923-10.832
75	35.862	22.523-45.236	15.235	10.523-19.862

CI: Confidence interval.

Table 5 Survival time of different effective tumor volume% groups before and after transcatheter arterial chemoembolization treatment

Percent (%)	< 0.414		≥ 0.414	
	Survival time (months)	95%CI	Survival time (months)	95%CI
25	3.235	1.523-5.862	10.523	6.523-14.862
50	9.235	5.862-12.523	17.862	13.926-20.635
75	15.235	10.235-31.523	29.635	19.862-72.523

CI: Confidence interval.

Table 6 Results of baseline effective tumor volume single factor and multi factor analysis using bias field correction

Variables	Control	Single factor		Multi-factor	
Age	Increase by 1	Hazard ratio	*P* value	Hazard ratio	*P* value
Pre-treatment ETV (cm³)	≥ 415 *vs* < 415	1.018 (0.982-1.036)	0.453	1.008 (0.964-1.032)	0.832
Gender	Female *vs* male	1.982 (1.212-3.236)	0.012	1.442 (0.823-2.558)	0.178
Child-Pugh classification	Class A *vs* (class B or C)	0.736 (0.438-1.264)	0.234	0.728 (0.416-1.282)	0.273
BCLC staging	Stage B *vs* (stage C or D)	0.423 (0.252-0.668)	< 0.001	0.432 (0.256-0.702)	< 0.001
Type of TACE	Control	0.523 (0.318-0.852)	0.013	0.538 (0.318-0.916)	0.023
Variables	Lipiodol *vs* DEB-TACE	1.178 (0.723-1.916)	0.548	1.016 (0.612-1.682)	0.976

ETV: Effective tumor volume; BCLC: Barcelona Clinic Liver Cancer; DEB-TACE: Drug-eluting bead transcatheter arterial chemoembolization.

In the analysis of the rate of ETV reduction (Table 7), univariate analysis showed that the rate of ETV reduction (≥ 41% *vs* < 41%, HR = 0.523, 95%CI: 0.346-0.918, $P = 0.018$), Child-Pugh classification (Class A *vs* class B or C, HR = 0.423, 95%CI: 0.252-0.668, $P < 0.001$), and BCLC staging (Stage B *vs* stage C or D, HR = 0.523, 95%CI: 0.318-0.852, $P = 0.013$) were significantly associated with patient prognosis. Multivariate analysis further confirmed that the rate of ETV reduction (HR = 0.412, 95%CI: 0.238-0.678, $P < 0.001$), Child-Pugh classification (HR = 0.298, 95%CI: 0.162-0.502, $P < 0.001$), and BCLC staging (HR = 0.578, 95%CI: 0.332-0.976, $P = 0.045$) were all independent prognostic factors. Similarly, age (HR = 1.008, 95%CI: 0.964-1.032, $P = 0.812$), gender (HR = 0.748, 95%CI: 0.432-1.328, $P = 0.324$), and type of TACE (HR = 0.832, 95%CI: 0.482-1.396, $P = 0.464$) did not show statistical significance in the multivariate analysis.

DISCUSSION

This study prospectively analyzed the application value of MRI bias field correction in volumetric imaging for assessing the therapeutic effects of TACE in iHCC, finding that bias field correction technology significantly improves the accuracy of volumetric measurements and provides more reliable quantitative indicators for predicting patient prognosis. This difference may stem from signal intensity variations caused by factors such as RF coil sensitivity non-uniformity, static field non-uniformity, and tissue magnetization rate differences during MRI imaging[14,15]. The improved N4 bias field correction algorithm can effectively compensate for these influences, providing volume data closer to reality[16]. This finding is consistent with previous studies reporting the impact of MRI bias fields on tumor volume measurements, but this study is the first to systematically validate the value of this technology in the assessment of TACE treatment for iHCC [17]. The study results showed that MRI bias field correction significantly affected the tumor volume measurements before and after TACE treatment, with the corrected ETV measurements being significantly lower than the uncorrected group (baseline ETV: 505.235 cm³ *vs* 825.632 cm³, $P < 0.001$; post-treatment ETV: 325.236 cm³ *vs* 632.523 cm³, $P < 0.001$), which is similar to the study by Koska *et al*[17].

Cox proportional hazards model analysis revealed that bias field correction significantly enhanced the predictive power of ETV as a prognostic indicator. The HR for the corrected baseline ETV (HR = 1.165) was significantly higher than the uncorrected group (HR = 1.063), indicating a stronger correlation between the corrected measurements and patient prognosis, similar to the study by Liu *et al*[18]. Notably, in terms of the percentage change in ETV, only the corrected group showed statistical significance (HR = 0.665, $P < 0.001$), while the uncorrected group failed to reflect this prognostic correlation (HR = 1.005, $P = 0.793$). This result indicates that bias field correction not only improves the accuracy of single measurements but, more importantly, enhances the reliability of longitudinal follow-up assessments[19,20]. The critical values determined by Martingale residual analysis (baseline ETV 412 cm³ and ETV reduction rate 40.253%) further support this conclusion, providing practical prognostic stratification standards for clinical practice[21].

Table 7 Single factor and multi factor analysis results of effective tumor volume% using bias field correction

Variable	Control	Single factor		Multi-factor	
		Hazard ratio	*P* value	Hazard ratio	*P* value
Age	Increase by 1	1.018 (0.982-1.036)	0.453	1.008 (0.964-1.032)	0.812
ETV reduction rate	≥ 41% *vs* < 41%	0.523 (0.346-0.918)	0.018	0.412 (0.238-0.678)	< 0.001
Gender	Female *vs* male	0.736 (0.438-1.264)	0.234	0.748 (0.432-1.328)	0.324
Child-Pugh	Class A *vs* (class B or C)	0.423 (0.252-0.668)	< 0.001	0.298 (0.162-0.502)	< 0.001
BCLC staging	Stage B *vs* (stage C or D)	0.523 (0.318-0.852)	0.013	0.578 (0.332-0.976)	0.045
TACE type	Lipiodol *vs* DEB-TACE	1.178 (0.723-1.916)	0.548	0.832 (0.482-1.396)	0.464

ETV: Effective tumor volume; BCLC: Barcelona Clinic Liver Cancer; DEB-TACE: Drug-eluting bead transcatheter arterial chemoembolization.

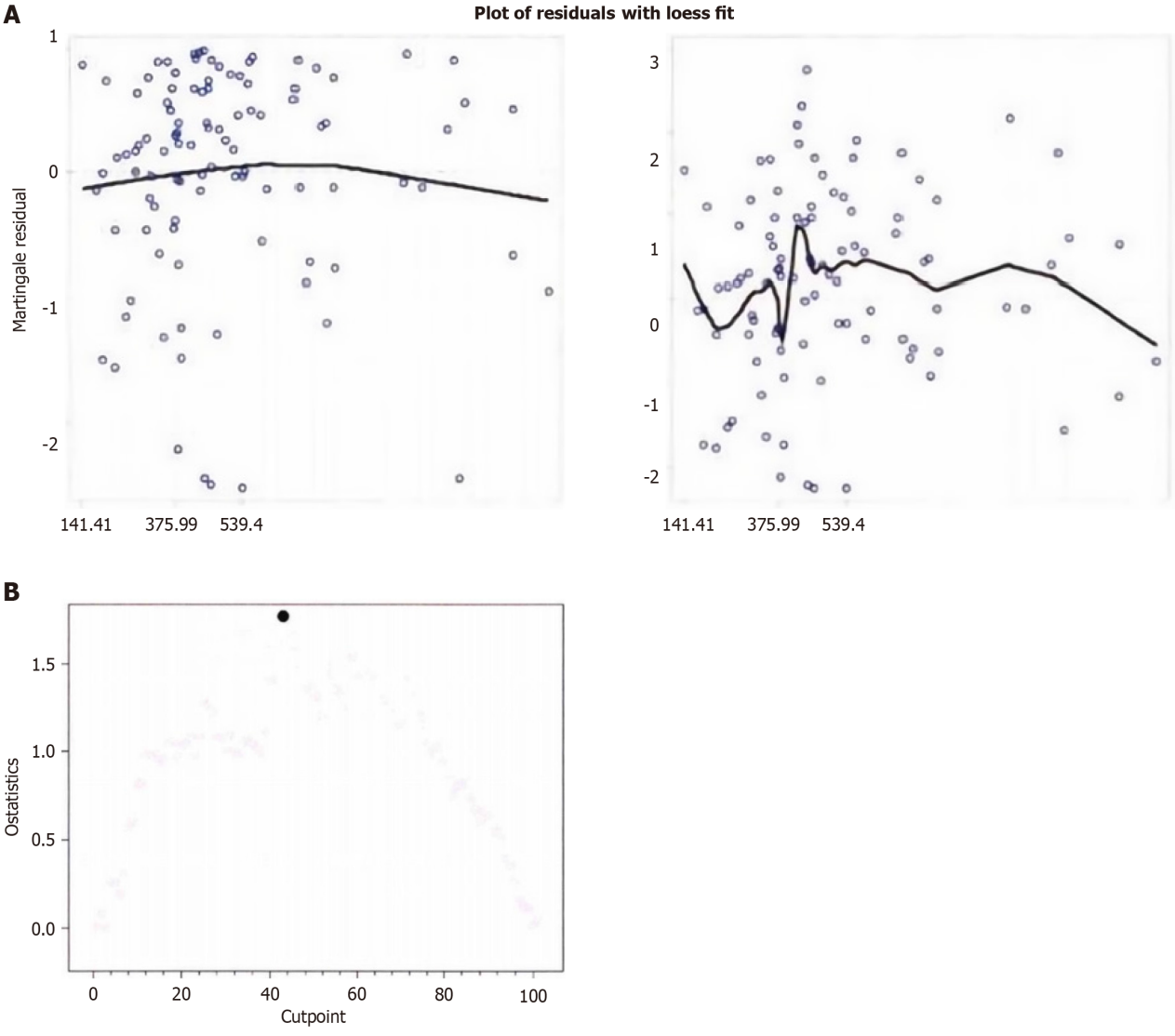


Figure 2 Enhanced tumor volume before the first transcatheter arterial chemoembolization treatment. A: Martingale residual local weighted scatterplot smoothing line of enhanced tumor volume before the first transcatheter arterial chemoembolization treatment; B: Enhanced tumor volume threshold before the first transcatheter arterial chemoembolization treatment corrected using bias field.

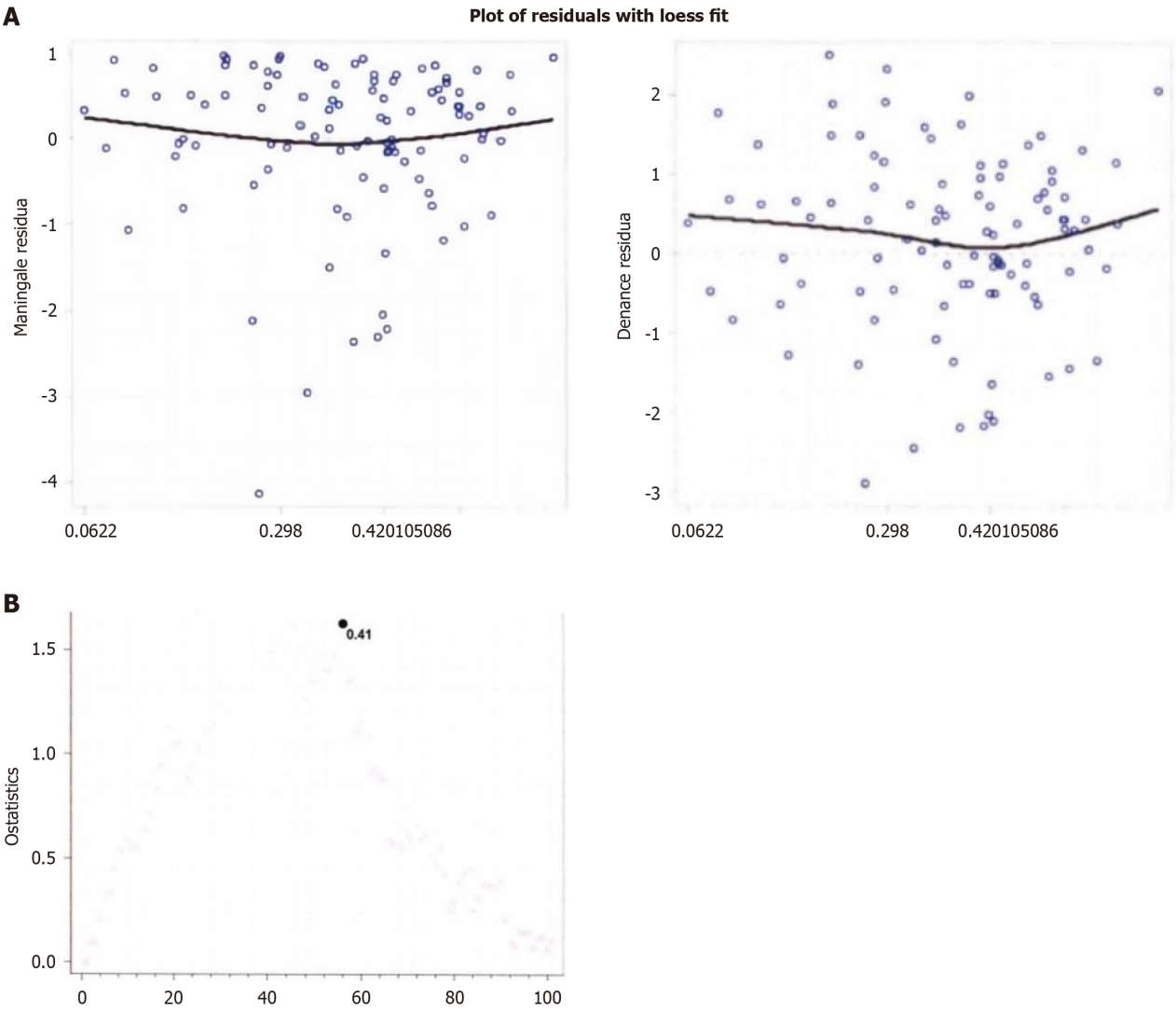


Figure 3 Local weighted scatterplot smoothing line of martingale residuals for enhanced tumor volume% before the first transcatheter arterial chemoembolization treatment. A: Martingale residual local weighted scatterplot smoothing line for enhanced tumor volume%; B: The critical value of enhanced tumor volume% before and after transcatheter arterial chemoembolization treatment with magnetic resonance bias field correction.

Survival analysis results indicated that patient grouping based on corrected ETV had significant prognostic discrimination. The group with baseline ETV < 415 cm³ showed a longer median survival time compared to the ≥ 415 cm³ group (18.523 months *vs* 8.926 months), and similarly, the group with an ETV reduction rate ≥ 41% also demonstrated better prognosis compared to the < 41% group (17.862 months *vs* 9.235 months). This survival difference was consistent at different percentile time points, reflecting good temporal stability of prognosis stratification based on corrected ETV[22,23]. Multivariate analysis further confirmed that the ETV reduction rate (HR = 0.412, $P < 0.001$), along with Child-Pugh classification (HR = 0.298, $P < 0.001$) and BCLC staging (HR = 0.578, $P = 0.045$), constitutes independent prognostic factors. This finding highlights the supplementary value of volumetric response assessment based on the existing staging system[24,25].

The clinical significance of the study results is mainly reflected in three aspects: First, the application of bias field correction technology provides a more reliable tool for accurately assessing TACE treatment responses, helping to overcome technical limitations in traditional volumetric measurements[26]; second, the prognostic stratification standards based on corrected ETV have good clinical practicality and can be used to guide the formulation and adjustment of treatment strategies[27]; third, the discovery of ETV reduction rate as an independent prognostic factor provides a new quantitative indicator for assessing TACE treatment effects[28]. Despite significant strides in hepatocellular carcinoma imaging assessment, our study confronts numerous challenges and limitations. As a single-center retrospective research, we must candidly acknowledge its inherent methodological deficiencies: Potential selection bias may restrict the generalizability of our findings, while the relatively brief follow-up period fails to comprehensively capture long-term prognostic changes, necessitating more sustained and in-depth observations. By focusing primarily on tumor volume measurements, we risk overlooking complex imaging features such as tumor heterogeneity, potentially underestimating the multifaceted value of imaging indicators in disease progression.

To transcend current research limitations, future studies should pursue improvements across multiple dimensions. The primary task is to construct a multicenter prospective research paradigm, expanding sample size, enhancing research

representativeness, and mitigating selection bias risks to provide more robust evidence. Simultaneously, we must actively integrate emerging imaging technologies like radiomics, moving beyond traditional volume measurements to comprehensively analyze tumor morphological characteristics and develop more dynamic and comprehensive prognostic assessment models. Research should not remain confined to technical dimensions but should explore the complex associations between imaging features and clinical prognosis, seeking pathways to personalized precision medicine. At the same time, it is recommended to incorporate bias field correction technology into routine imaging assessment processes to improve the accuracy of clinical decision-making.

Specifically, future research should prioritize four key strategic areas: Future investigations must transcend the limitations of single-center, retrospective studies by implementing robust, multicenter prospective research frameworks. This approach will enhance sample diversity, reduce potential selection biases, and improve the generalizability of research findings. Expanding sample size and incorporating diverse patient populations will provide more comprehensive and representative insights into hepatocellular carcinoma imaging assessment. The convergence of advanced imaging technologies, computational approaches, and clinical insights promises to revolutionize our understanding and management of hepatocellular carcinoma, transforming how we conceptualize and treat this complex disease.

CONCLUSION

In summary, this study confirms the important value of volumetric imaging based on MRI bias field correction in assessing the TACE treatment effects of iHCC, providing new technical means and clinical evidence to improve the accuracy of treatment response assessment and the reliability of prognostic prediction. These findings are of significant guidance for optimizing personalized treatment strategies for patients with invasive liver cancer.

FOOTNOTES

Author contributions: Liu K and Li Y conceived and designed the study; Li JB and Wang Y collected and curated the data; Liu K and Li JB performed the methodology and formal analysis, and drafted the manuscript; Wang Y and Li Y acted as translators, and critically revised it for important intellectual content; Li Y supervised the entire project; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Construction of a risk prediction model for postoperative cognitive dysfunction in colorectal cancer patients

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Abstract

BACKGROUND

Colorectal cancer (CRC) is one of the most prevalent and lethal malignant tumors worldwide. Currently, surgical intervention was the primary treatment modality for CRC. However, increasing studies have revealed that CRC patients may experience postoperative cognitive dysfunction (POCD).

AIM

To establish a risk prediction model for POCD in CRC patients and investigate the preventive value of dexmedetomidine (DEX).

METHODS

A retrospective analysis was conducted on clinical data from 140 CRC patients who underwent surgery at the People's Hospital of Qian Nan from February 2020 to May 2024. Patients were allocated into a modeling group (n = 98) and a validation group (n = 42) in a 7:3 ratio. General clinical data were collected. Additionally, in the modeling group, patients who received DEX preoperatively were incorporated into the observation group (n = 54), while those who did not were placed in the control group (n = 44). The incidence of POCD was recorded for both cohorts. Data analysis was performed using statistical product and service solutions 20.0, with t-tests or χ^2 tests employed for group comparisons based on the data type. Least absolute shrinkage and selection operator regression was applied to identify influencing factors and reduce the impact of multicollinear predictors among variables. Multivariate analysis was carried out using Logistic regression. Based on the identified risk factors, a risk prediction model for POCD in CRC patients was developed, and the predictive value of these risk factors was evaluated.

RESULTS

Significant differences were observed between the cognitive dysfunction group

and the non-cognitive dysfunction group in diabetes status, alcohol consumption, years of education, anesthesia duration, intraoperative blood loss, intraoperative hypoxemia, use of DEX during surgery, intraoperative use of vasoactive drugs, surgical time, systemic inflammatory response syndrome (SIRS) score ($P < 0.05$). Multivariate Logistic regression analysis identified that diabetes [odds ratio (OR) = 4.679, 95% confidence interval (CI) = 1.382-15.833], alcohol consumption (OR = 5.058, 95%CI: 1.255-20.380), intraoperative hypoxemia (OR = 4.697, 95%CI: 1.380-15.991), no use of DEX during surgery (OR = 3.931, 95%CI: 1.383-11.175), surgery duration ≥ 90 minutes (OR = 4.894, 95%CI: 1.377-17.394), and a SIRS score ≥ 3 (OR = 4.133, 95%CI: 1.323-12.907) were independent risk factors for POCD in CRC patients ($P < 0.05$). A risk prediction model for POCD was constructed using diabetes, alcohol consumption, intraoperative hypoxemia, non-use of DEX during surgery, surgery duration, and SIRS score as factors. A receiver operator characteristic curve analysis of these factors revealed the model's predictive sensitivity (88.56%), specificity (70.64%), and area under the curve (AUC) (AUC = 0.852, 95%CI: 0.773-0.919). The model was validated using 42 CRC patients who met the inclusion criteria, demonstrating sensitivity (80.77%), specificity (81.25%), and accuracy (80.95%), and AUC (0.805) in diagnosing cognitive impairment, with a 95%CI: 0.635-0.896.

CONCLUSION

Logistic regression analysis identified that diabetes, alcohol consumption, intraoperative hypoxemia, non-use of DEX during surgery, surgery duration, and SIRS score vigorously influenced the occurrence of POCD. The risk prediction model based on these factors demonstrated good predictive performance for POCD in CRC individuals. This study offers valuable insights for clinical practice and contributes to the prevention and management of POCD under CRC circumstances.

Key Words: Colorectal cancer; Postoperative; Cognitive dysfunction; Anesthesia; Risk prediction model; Dexmedetomidine; Preventive value

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Core Tip: This study developed a risk prediction model for postoperative cognitive dysfunction (POCD) in colorectal cancer (CRC) patients, identifying key risk factors such as diabetes, alcohol consumption, intraoperative hypoxemia, non-use of dexmedetomidine (DEX), surgery duration ≥ 90 minutes, and a systemic inflammatory response syndrome score ≥ 3. The model demonstrated good predictive performance, with high sensitivity and specificity, and highlights the preventive value of DEX in reducing POCD incidence. This research provides valuable insights for improving POCD prevention and management in CRC patients.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent and lethal malignant tumors worldwide. According to the International Agency for Research on Cancer, CRC ranks third among all cancer types, with incidence rates steadily increasing over the past few decades[1]. Advances in medical technology and the promotion of early screening improves early diagnosis rate, making surgical intervention as the primary treatment modality for CRC[2]. Nevertheless, surgery exerts a huge impact on patients both physiologically and psychologically, particularly concerning postoperative cognitive function. An increasing number of studies have revealed that CRC patients may experience cognitive impairments post-surgery, which adversely affects their quality of life, their postoperative recovery and overall prognosis[3-5]. Recent studies have shown growing interest in postoperative cognitive dysfunction (POCD), identifying factors such as surgery, anesthesia, length of hospitalization, and complications as potential contributors. Additionally, patient-specific characteristics including age, gender, underlying health conditions, and psychological status are also considered potential risk factors for developing cognitive impairments postoperatively[6]. Therefore, developing a risk prediction model specifically for POCD under CRC conditions can help identify those at high risk, enabling timely interventions and management to attenuate the incidence of POCD.

In the realm of preventing POCD, dexmedetomidine (DEX) has emerged as a novel sedative, widely used in surgical anesthesia due to its effective sedation and analgesic properties[7]. Studies have demonstrated that DEX reduce the amount of anesthetic required, minimizes postoperative complications, and promotes recovery[8]. Preliminary clinical studies suggests that DEX may offer protective effects on postoperative cognitive function. However, systematic and large-scale studies are still needed to validate its efficacy and elucidate its mechanisms[9]. Thus, exploring the preventive value of DEX against POCD in CRC patients is of significant clinical relevance.

This research retrospectively analyzed the data from 140 CRC patients to evaluate the preventive effects of DEX on POCD. It also examined the differences in baseline characteristics between patients with and without POCD to identify the factors influencing postoperative cognitive function in CRC patients. A risk prediction model was subsequently developed to provide new insights and evidence for postoperative management in these patients while fostering a deeper understanding of POCD and its interventions.

MATERIALS AND METHODS

Materials and methods

General data: A stratified multi-stage sampling method was adopted to estimate the sample size. In the sample mean formula $N = (U \times \alpha \times \sigma/\delta) \times 2$, U represents the value corresponding to the significance level α, σ denotes the population standard deviation, and δ is the allowable error. With the use of this formula, a preliminary experiment yielded the following parameters: $\Sigma = 1.06$, $\alpha = 0.07$, and $\delta = 0.1$. This calculation resulted in a sample size of 130. Considering a sampling error of 10% to 13%, the sample size was enlarged to 140 cases. Researchers obtained written informed consent from all patients prior to their participation in the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable local regulatory requirements. The study was approved by the People's Hospital of Qian Nan ethics committee (No. 2024-qnzy-25).

Inclusion criteria: (1) Diagnosed with CRC[10]; (2) Complete general clinical data; (3) American Society of Anesthesiologists (ASA) classification of I to III; (4) No evidence of cancer metastasis or spreading; and (5) Mentally stable individuals.

Exclusion criteria: (1) Pre-existing cognitive dysfunction; (2) History of traumatic brain injury; (3) Patients who had undergone major surgery within the last three months; and (4) Presence of other malignant tumors.

Methods and observation indicators

Preventive treatment: Prior to the induction of anesthesia, DEX, provided by Jiangsu Hengrui Medicine Co., Ltd., was intravenously administered at a dosage of 0.5 μg/kg. Following induction, a continuous infusion at a rate of 0.3 μg/kg/hour was maintained until 30 minutes before the end of the procedure. All participants received sufentanil at doses of 0.3-0.4 μg/kg, propofol at 1.0-2.0 mg/kg, and rocuronium at 0.6 mg/kg for induction, followed by orotracheal intubation for mechanical ventilation. During the procedure, propofol was administered intravenously at a rate of 4-8 mg/kg/hour, along with remifentanil at 0.05-0.20 μg/kg/minute to sustain anesthesia, while intermittent intravenous administration of rocuronium was implemented to maintain muscle relaxation.

Cognitive dysfunction: Cognitive function in patients was assessed through the mini-mental state examination (MMSE) scale[11], which evaluates various domains comprising language ability, attention, recall, memory, orientation, and calculation skills. MMSE consists of 30 items, with a maximum total score of 30, and the assessment needs to be completed within 8 minutes. A score of ≤ 18 is considered indicative of severe cognitive impairment, 19-23 reflects moderate cognitive impairment, 24-27 signifies mild cognitive dysfunction, and scores of 28-30 indicate no cognitive impairment. The MMSE scale is assessed by a trained attending physician before and on the first postoperative day.

Multivariate analysis

Patient data regarding gender, age, body mass index (BMI), ASA classification, hypertension, tumor node metastasis (TNM) staging, smoking history, marital status, intraoperative use of vasoactive drugs, tumor location, diabetes, alcohol consumption, years of education, anesthesia duration, intraoperative blood loss, intraoperative hypoxemia, use of DEX, surgery duration, systemic inflammatory response syndrome (SIRS) score, and postoperative fasting duration were recorded and analyzed *via* electronic medical records. The SIRS score was calculated as *per* the following criteria: A temperature > 38 °C or < 36 °C scores 1 point; A heart rate > 90 beats *per* minute scores 1 point; A respiratory rate > 20 breaths *per* minute or arterial blood gas analysis denoting partial pressure of carbon dioxide < 32 mmHg scores 1 point; and A white blood cell count > 12×10^9/L or < 4×10^9/L, or > 10% immature cells scores 1 point. A Postoperative 24-hour assessment of systemic inflammatory response using SIRS scores. SIRS score of 0 suggests no inflammatory response, 1-2 indicates mild inflammatory response, and 3-4 signifies moderate to severe inflammatory response[12]. Logistic regression analysis was taken to confirm various factors influencing POCD in CRC patients.

Construction of a risk prediction model

Based on the identified risk factors, a risk prediction model for POCD in CRC patients was established. The partial regression coefficients obtained from the Logistic regression analysis were incorporated into the prediction model. The predictive performance of the model was confirmed through the area under the receiver operating characteristic (ROC) curve (AUC), with an AUC value exceeding 0.7 regarded as indicative of good predictive performance for the endpoint event.

Statistical analysis

Statistical product and service solutions 20.0 software (SPSS Inc., Chicago, IL, United States) was introduced for statistical analysis. The Shapiro-Wilk test is used to assess normality. For unordered categorical data, the χ^2 test or Fisher's precise

test was employed, while measurement data were reported as (mean ± SD) and analyzed *via* *t*-tests. In the univariate analysis, variables with $P < 0.05$ are considered potential predictors. To refine these predictors, a multicollinearity test was conducted and least absolute shrinkage and selection operator (LASSO) regression was employed for variable selection using R version 4.0.5. Multivariate analysis was conducted through Logistic regression to develop a risk prediction model based on identified risk factors, and cross-validation was utilized to determine the model's predictive performance. Using GraphPad Prism software (GraphPad Software, Inc., San Diego, CA, United States), we plotted calibration curves to assess the efficacy of the risk prediction model in postoperative cognitive impairment among patients with rectal cancer. Additionally, we utilized R statistical software (University of Auckland, New Zealand) to plot decision curve analysis curves to evaluate the clinical applicability of the risk prediction model. A P value of < 0.05 was deemed to hold statistical significance.

RESULTS

Baseline data

The sampling period lasted from February 2020 to May 2024. All 140 CRC patients underwent surgical treatment at The People's Hospital of Qian Nan, and they were divided into a modeling group (n = 98) and a validation group (n = 42) in a 7:3 ratio. No significant differences in baseline characteristics were observed between the two cohorts ($P > 0.05$), as illustrated in Table 1. Additionally, in the modeling group, patients receiving DEX preoperatively were incorporated into the observation group (n = 54), whereas those not subjected to DEX were placed in the control cohort (n = 44). No remarkable differences were found in baseline data between the two cohorts ($P > 0.05$), as displayed in Table 2.

Univariate analysis of POCD in CRC patients

Out of 98 patients, 37 exhibited POCD, culminating in an incidence rate of 37.76%, and they were classified into the cognitive dysfunction cohort. The remaining 61 patients, who demonstrated normal cognitive function, were placed in the non-cognitive dysfunction cohort.

A comparison of general clinical data between the two cohorts displayed no significant differences in terms of gender, age, BMI, ASA classification, hypertension, TNM staging, smoking history, marital status, tumor location and postoperative fasting duration ($P > 0.05$). Nevertheless, significant differences were observed between the two cohorts regarding diabetes, alcohol consumption, years of education, anesthesia duration, intraoperative blood loss, intraoperative hypoxemia, use of DEX during surgery, use of vasoactive agents during surgery, surgical time, SIRS scores ($P < 0.05$), as illustrated in Table 3.

Multivariate analysis of factors influencing POCD in CRC patients

As *per* the methods outlined in Table 2, values were assigned to the aforementioned single factors and incorporated into the Logistic regression model for multivariate analysis. Before multivariate analysis, we used LASSO regression to select influencing factors and eliminate multicollinearity among variables. The data demonstrated that diabetes, alcohol consumption, intraoperative hypoxemia, non-use of DEX during surgery, surgical duration of ≥ 90 minutes, and SIRS scores of ≥ 3 were identified as independent risk factors for POCD in CRC patients ($P < 0.05$), as exhibited in Table 4 and Table 5.

Establishment of a risk prediction model for POCD in CRC patients

A risk prediction model for POCD in CRC individuals was developed based on the factors of diabetes, alcohol consumption, intraoperative hypoxemia, non-use of DEX during surgery, surgical duration, and SIRS scores. The probability formula is $P = 1/[1 + e^{(1.543 \times \text{diabetes} + 1.621 \times \text{alcohol consumption} + 1.547 \times \text{intraoperative hypoxemia} + 1.369 \times \text{non-use of DEX} + 1.588 \times \text{surgical duration} + 1.419 \times \text{SIRS score})}]$. ROC curve analysis of these risk factors revealed a sensitivity of 88.56% and specificity of 70.64% for predicting POCD, with an AUC of 0.852, as presented in Figure 1A.

Model validation

This investigation encompassed 42 CRC individuals from the validation cohort who met the inclusion criteria. The aforementioned model was applied for prediction, using cross-validation. Among these 42 patients, 26 actually experienced cognitive impairment, while the model identified 21 cases of cognitive impairment. The model demonstrated a sensitivity of 80.77%, a specificity of 81.25%, and an accuracy of 80.95% in predicting cognitive dysfunction, AUC was 0.805, with a 95%CI: 0.635 to 0.896, as shown in Figure 1B and Table 6. Additionally, the results of the calibration curve analysis indicated that the predictive model's calibration curve for postoperative cognitive impairment closely matched the ideal curve for both the modeling group and the validation group of CRC patients (Figure 2). A decision curve analysis was conducted to assess the model's clinical effectiveness. The results showed that the model provided better clinical benefits when the high-risk threshold probability ranged from 0.17 to 0.89, as demonstrated in Figure 3.

DISCUSSION

CRC is one of the most prevalent malignant tumors worldwide, and surgical treatment is a common clinical intervention. Nonetheless, increasing evidence suggests that patients with CRC may undergo cognitive impairment postoperatively,

Table 1 General data, mean ± SD

General data	Modeling group (*n* = 98)	Validation group (*n* = 42)	χ^2/t	*P* value
Gender			0.136	0.712
Male	48	22		
Female	50	20		
Age (years)	56.12 ± 6.33	56.23 ± 6.27	0.094	0.925
ASA classification			1.979	0.159
Class I-II	41	23		
Class III	57	19		
TNM staging			0.510	0.775
Stage I	38	19		
Stage II	29	11		
Stage III	31	12		

TNM: Tumor node metastasis; ASA: American Society of Anesthesiologists.

Table 2 Baseline data, mean ± SD

Baseline data	Observation group (*n* = 54)	Control group (*n* = 44)	χ^2/t	*P* value
Gender			0.347	0.556
Male	25	23		
Female	29	21		
Age (years)	56.08 ± 6.23	56.04 ± 6.17	0.032	0.975
ASA classification			0.059	0.807
Class I-II	22	19		
Class III	32	25		
TNM staging			0.298	0.862
Stage I	21	17		
Stage II	17	12		
Stage III	16	15		

TNM: Tumor node metastasis; ASA: American Society of Anesthesiologists.

which can adversely affect their quality of life and recovery process[13]. The mechanisms behind POCD are complex and may involve factors such as postoperative inflammatory responses, the use of anesthetic agents, and the overall health status of the patients[14]. Therefore, early identification and prediction of these risk factors are crucial for improving outcomes. Recently, DEX has emerged as a novel anesthetic that shows promise in mitigating postoperative delirium and improving cognitive function[15,16]. This research aims to develop a risk prediction model that incorporates multiple clinical, preoperative, and postoperative factors, while also assessing the preventive value of DEX for POCD under CRC circumstances, ultimately providing valuable insights for clinical management and treatment strategies.

Here, it was found that 37 out of 98 patients experienced POCD, resulting in an incidence rate of 37.76%, consistent with previous findings[17]. Despite the use of DEX, a residual risk of cognitive impairment remains, indicating that while DEX can partially mitigate these issues, it cannot entirely suppress POCD in CRC patients, making it necessary to observe, evaluate, and give strategies to lower the risk of cognitive dysfunction. Logistic regression analysis identified diabetes, alcohol consumption, intraoperative hypoxemia, non-use of DEX, surgical duration of 90 minutes or more, and SIRS scores of 3 or higher as independent risk factors for POCD.

This analysis revealed several factors associated with POCD: (1) Diabetes often results in fluctuating blood glucose levels, leading to inadequate or excessive energy supply to the brain, adversely affecting neurological function and cognitive abilities. Postoperative conditions, particularly those involving anesthesia and surgical stress, can exacerbate these fluctuations, increasing the risk of cognitive dysfunction[18]. Furthermore, diabetes is associated with a chronic

Table 3 Univariate analysis of postoperative cognitive dysfunction in colorectal cancer patients, mean ± SD

General data	Cognitive dysfunction group (*n* = 37)	Non-cognitive dysfunction group (*n* = 61)	χ^2/t	*P* value
Gender			0.219	0.640
Male	17	31		
Female	20	30		
Age (years)	56.44 ± 6.12	55.83 ± 7.12	0.433	0.666
BMI			1.255	0.263
≥ 24 kg/m^2	11	25		
< 24 kg/m^2	26	36		
ASA classification			1.097	0.295
Class I-II	13	28		
Class III	24	33		
Hypertension			0.188	0.665
Presence	10	19		
Absence	27	42		
Diabetes			4.353	0.037
Presence	25	28		
Absence	12	33		
Alcohol consumption			4.183	0.041
Presence	26	30		
Absence	11	31		
TNM staging			2.834	0.242
Stage I	17	21		
Stage II	12	17		
Stage III	8	23		
Smoking history			0.414	0.520
Presence	11	22		
Absence	26	39		
Education (years)			4.389	0.036
≥ 10 years	22	23		
< 10 years	15	38		
Marital status			0.794	0.373
Married	13	27		
Unmarried/widowed	24	34		
Anesthesia duration			5.143	0.023
≥ 4 hours	25	22		
< 4 hours	12	29		
Intraoperative blood loss			4.832	0.028
≥ 300 mL	26	29		
< 300 mL	11	32		
Intraoperative hypoxemia			8.543	0.003
Presence	27	26		

Absence	10	35		
Use of DEX during surgery			9.770	0.002
Absence	26	23		
Presence	11	38		
Use of vasoactive agents during surgery			4.353	0.037
Presence	25	28		
Absence	12	33		
Surgical duration			7.368	0.007
≥ 90 minutes	29	31		
< 90 minutes	8	30		
Tumor location			0.149	0.928
Proximal colon	13	22		
Distal colon	11	16		
Rectum	13	23		
SIRS scores			5.939	0.015
≥ 3 points	28	31		
< 3 points	9	30		
Postoperative fasting duration			0.103	0.748
≥ 3 days	20	35		
< 3 days	17	26		

BMI: Body mass index; DEX: Dexmedetomidine; SIRS: Systemic inflammatory response syndrome; TNM: Tumor node metastasis; ASA: American Society of Anesthesiologists.

Table 4 Assignment method

Factors	Assignment
Diabetes	1: Presence; 0: Absence
Alcohol consumption	1: Presence; 0: Absence
Years of education	1: ≥ 10 years; 0: < 10 years
Anesthesia duration	1: ≥ 4 hours; 0: < 4 hours
Intraoperative blood loss	1: ≥ 300 mL; 0: < 300 mL
Intraoperative hypoxemia	1: Presence; 0: Absence
Intraoperative use of DEX	1: Absence; 0: Presence
Surgical time	1: ≥ 90 minutes; 0: < 90 minutes
Intraoperative use of vasoactive drugs	1: Absence; 0: Presence
SIRS score	1: ≥ 3 points; 0: < 3 points

DEX: Dexmedetomidine; SIRS: Systemic inflammatory response syndrome.

inflammatory state, where augmented release of inflammatory factors can negatively affect the nervous system. Chronic inflammation has been linked to cognitive decline, which may exacerbate this risk of cognitive impairment in diabetic patients[19]. Therefore, it is essential to closely monitor blood glucose levels in CRC patients both preoperatively and postoperatively. Appropriate pharmacological interventions should be implemented to maintain stable blood glucose in diabetic patients, attenuating the likelihood of cognitive impairment; (2) Chronic heavy drinking can damage neurological function, including cognitive decline and memory loss. Alcohol directly impacts brain structure and function, causing neuronal damage and even cell death, thus affecting postoperative cognitive performance[20]. Moreover, alcohol can affect vascular function, leading to reduced cerebral blood flow and potentially resulting in

Table 5 Risk factors of postoperative cognitive dysfunction in colorectal cancer patients

Factors	β value	SE value	χ^2 value	OR	95%CI	*P* value
Diabetes	1.613	0.713	5.118	5.018	1.241-20.297	0.024
Alcohol consumption	1.589	0.623	6.505	4.899	1.445-16.611	0.011
Years of education	1.317	0.723	3.318	3.732	0.905-15.396	0.069
Anesthesia duration	1.369	0.933	2.153	3.931	0.631-24.476	0.143
Intraoperative blood loss	1.283	0.689	3.467	3.607	0.935-13.922	0.063
Intraoperative hypoxemia	1.592	0.634	6.305	4.914	1.418-17.024	0.012
Non-use of DEX during surgery	1.337	0.629	4.518	3.808	1.110-13.064	0.034
Intraoperative use of vasoactive drugs	1.371	0.735	3.479	3.939	0.933-16.637	0.063
Surgical time	1.592	0.633	6.325	4.914	1.421-16.991	0.012
SIRS scores	1.432	0.588	5.931	4.187	1.322-13.256	0.015

DEX: Dexmedetomidine; SIRS: Systemic inflammatory response syndrome; OR: Odds ratio; CI: Confidence interval.

Table 6 Model validation

Model		Actual cognitive dysfunction		
		Positive	Negative	Total
Prediction of cognitive dysfunction	Positive	21	4	25
	Negative	5	12	17
	Total	26	16	42

inadequate oxygen supply to the brain following surgery, which elevate the risk of cognitive impairment in postoperative patients[21,22]; (3) Hypoxemia directly causes insufficient oxygen supply to brain, disrupting the metabolism and function of neuronal cells, which results in neuronal damage. The brain, which has a high demand for oxygen, is vulnerable to prolonged hypoxic conditions[23]. Intraoperative hypoxemia can also affect the brain's neuroplasticity, which refers to the ability of neural networks to reorganize and recover function. An imbalance in this neuroplasticity may result in delayed or incomplete recovery of cognitive function postoperatively[24]; (4) DEX, a steroid with potent anti-inflammatory properties, is often implicated in the pathogenesis of POCD triggered by surgery. The absence of DEX use may give rise to a more pronounced inflammatory response post-surgery, which can negatively influence brain function[25]. When DEX was not applied, stress response induced by surgery could be out of control, leading to excessive neuroendocrine activation postoperatively, thereby heightening the risk of POCD[26]. Moreover, DEX has demonstrated neuroprotective effects by reducing neuronal apoptosis and mitigating brain damage. The omission of DEX during surgery may cause the loss of this neuroprotective benefits, further impacting postoperative cognitive function[27,28]. Therefore, in clinical practice, the preventive use of DEX preoperatively is necessary to attenuate the incidence of POCD. Besides, a recent study specifically studied the underlying mechanism by which DEX prevent POCD. They found that DEX upregulated *PINK1* in aged rats, a key regulator of mitophagy, thereby enhancing mitochondrial autophagy and reducing caspase-1/11-*GSDMD*-mediated pyroptosis in neurons[29], providing a clear rationale for the neuroprotective effects of DEX and explaining the lower incidence of POCD after DEX use; (5) Prolonged surgeries are often accompanied by extended periods of general anesthesia, which may impact the central nervous system and contribute to POCD postoperatively. The extended duration alters the metabolism and clearance of anesthetic drugs, augmenting the risk of POCD[30,31]. Longer surgery duration may indicate heightened physiological stress during the procedure, including blood loss, hypoxia, and inflammatory responses. These stressors can exert a negative impact on brain function, culminating in cognitive decline following surgery[32]; and (6) The SIRS, characterized by the release of inflammatory factors such as cytokines and interleukins, could be assessed using the SIRS score. The accumulation of these substances in the brain can impair neuronal function, leading to cognitive decline[33,34]. The onset of SIRS may also be followed by a drop in blood pressure and inadequate tissue perfusion, which can result in hypoxia and insufficient nutrient supply to the brain, causing cognitive impairment, especially during postoperative recovery[35,36].

Based on our findings, we propose the following targeted clinical recommendations for addressing independent risk factors associated with POCD in CRC patients: For diabetic patients, it is essential to strengthen preoperative and postoperative blood glucose management, employing individualized strategies to control glucose fluctuations. For patients with alcohol dependence, preoperative interventions should include alcohol cessation or reduction, and postoperative cognitive function should be closely monitored to mitigate long-term neurological damage. Besides, DEX should be administrated prophylactically during the preoperative and intraoperative period based on patient-specific

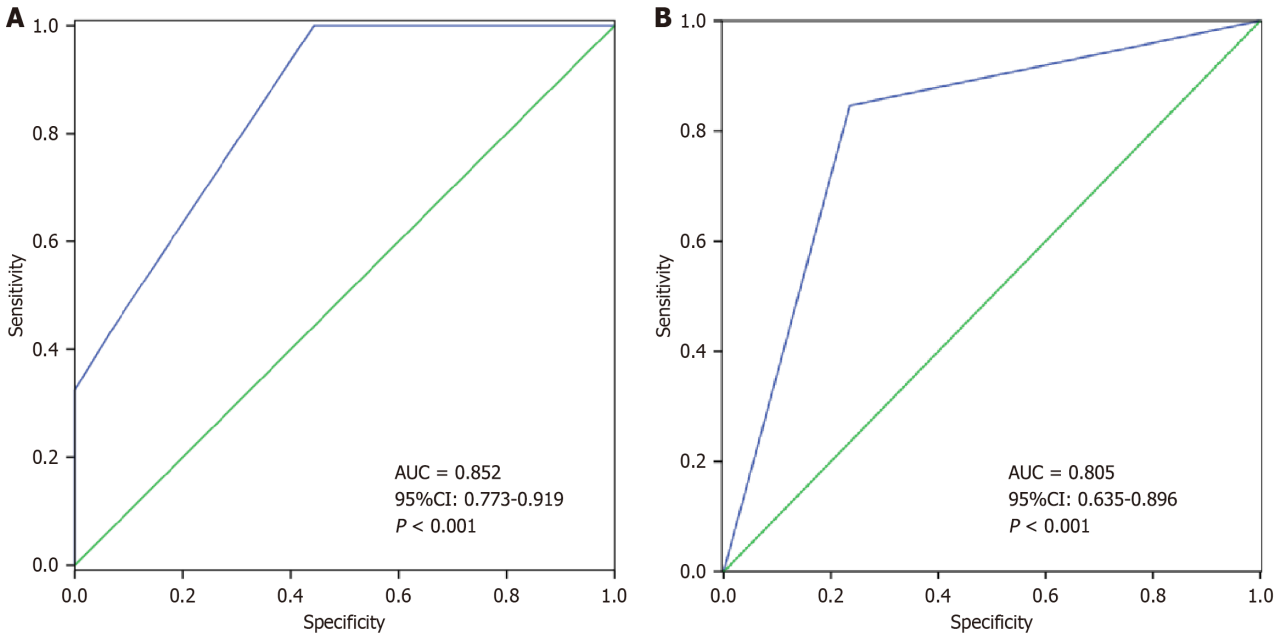


Figure 1 Receiver operating characteristic curve. A: The risk prediction model for Receiver operating characteristic in colorectal cancer patients; B: Postoperative cognitive impairment in the validation group of colorectal cancer patients using a risk prediction model. AUC: Area under the curve; CI: Confidence interval.

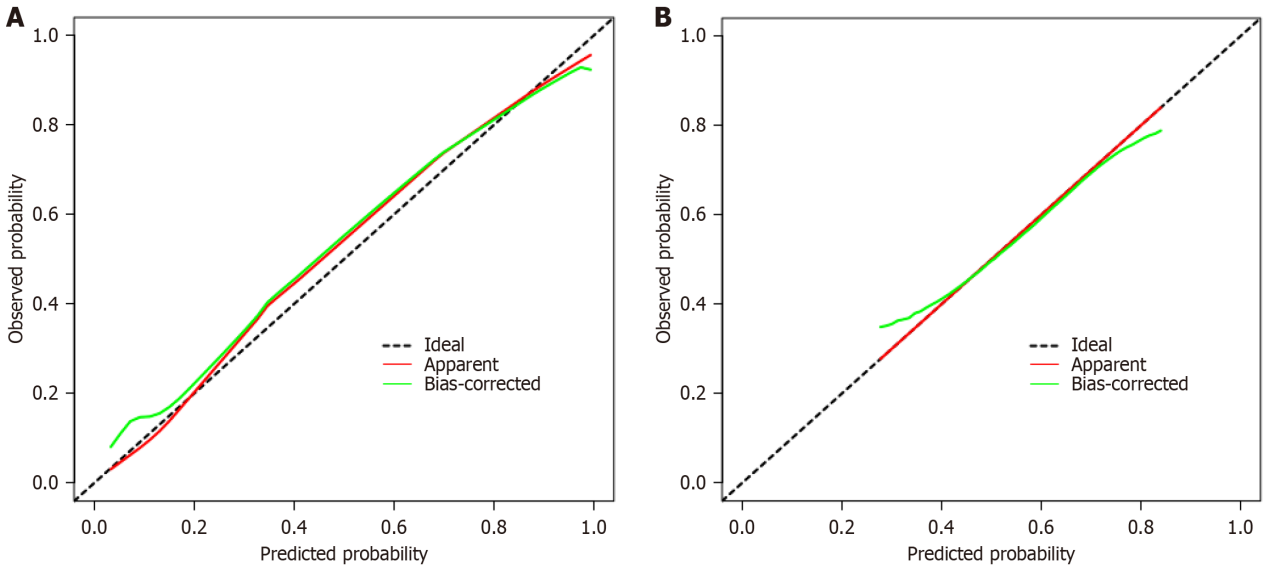


Figure 2 Calibration curve. A: The predictive model for postoperative cognitive impairment in colorectal cancer patients in the modeling group; B: The predictive model for postoperative cognitive impairment in colorectal cancer patients in the validation group.

conditions. Optimizing the dosage and timing of DEX administration can suppress systemic inflammatory responses, reduce neuronal apoptosis, and enhance cognitive protection. Lastly, for patients with high SIRS scores, their inflammatory status should be closely monitored. By implementing these comprehensive intervention measures, the risk of POCD in CRC patients can be significantly reduced, enhancing postoperative recovery quality and improving long-term patient satisfaction.

Here, a risk prediction model was developed based on various risk factors, including diabetes, alcohol consumption, intraoperative hypoxemia, use of DEX during surgery, surgery duration, and SIRS score. These factors were discovered to have predictive value for POCD in CRC patients. This study offers valuable insights for clinicians, especially in the management of high-risk CRC patients. By identifying and addressing the aforementioned risk factors, the incidence of POCD can be effectively reduced. Additionally, a group of 42 CRC patients who met the inclusion criteria was selected for validation *via* a cross-validation method. The model demonstrated a sensitivity of 80.77%, a specificity of 75.00%, and an accuracy of 78.57% in forecasting cognitive impairment, further confirming its effectiveness in assessing the likelihood of POCD in this patient population. This study, in comparison to previous research on POCD predictive models[37], has significantly enhanced predictive performance by introducing the use of DEX and SIRS scores as new risk factors.

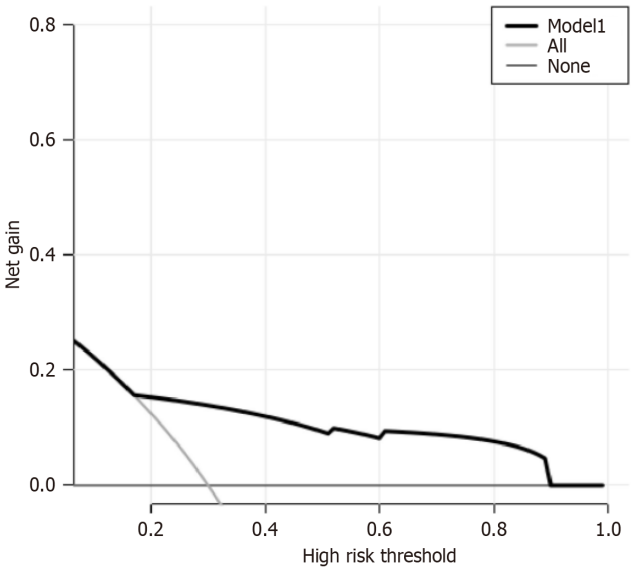


Figure 3 Decision curve analysis curve of the risk prediction model for predicting postoperative cognitive impairment in colorectal cancer patients in the modeling group.

Additionally, this study validated the known risk factors for POCD, including diabetes, alcohol consumption, intraoperative hypoxemia, and surgery lasting ≥ 90 minutes. Notably, it identified the independent impact of DEX use and SIRS scores on POCD. These findings not only improve the accuracy of POCD prediction but also provide additional early intervention points, having broad clinical application value, particularly for CRC patients.

Nevertheless, this study has several limitations, including potential biases arising from its retrospective design, limited sample size impacting the generalizability of the results, data originating from a single hospital restricting external validity, and non-standardized administration of DEX potentially affecting outcome consistency. Additionally, model validation was conducted on only a subset of the data, and key variables such as preoperative cognitive assessments and detailed drug regimens were not included. Addressing these limitations, future efforts should focus on conducting larger, prospective, multicenter studies to enhance the robustness and applicability of the findings. Emphasis should also be placed on incorporating key variables to further refine the model's accuracy and clinical utility.

CONCLUSION

In conclusion, the preoperative administration of DEX demonstrated potential in preventing POCD. The risk prediction model incorporates factors such as diabetes, alcohol consumption, intraoperative hypoxemia, DEX usage during surgery, operation time ≥ 90 minutes, and SIRS score ≥ 3 demonstrated good predictive performance for POCD among CRC patients. Identifying high-risk patients preoperatively and implementing preventive measures can provide valuable clinical guidance, ameliorating cognitive outcomes for these patients. These recommendations and interventions will help reduce the occurrence of postoperative cognitive impairment and enhance the overall therapeutic efficacy for patients.

FOOTNOTES

Author contributions: Zheng ZP and He K contributed to the conception and design of the study, data acquisition and analysis, and analyzed the data and wrote the manuscript; Zhang YG assisted with study design; Long MB assisted with data collection; Ji KQ performed data analysis; Peng JY and He K supervised and coordinated the project.

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ORIGINAL ARTICLE

Retrospective Study

Predictive factors for liver abscess liquefaction degree based on clinical, laboratory, and computed tomography data

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Abstract

BACKGROUND

Effective management of liver abscess depends on timely drainage, which is influenced by the liquefaction degree. Identifying predictive factors is crucial for guiding clinical decisions.

AIM

To investigate the predictive factors of liver abscess liquefaction and develop a predictive model to guide optimal timing of percutaneous drainage.

METHODS

This retrospective study included 110 patients with pyogenic liver abscesses who underwent percutaneous catheter drainage. Patients were divided into a poor liquefaction group (n = 28) and a well liquefaction group (n = 82) based on the ratio of postoperative 24-hour drainage volume to abscess volume, using a cutoff value of 0.3. Clinical characteristics, laboratory indicators, and computed tomography imaging features were compared. A predictive model was constructed using logistic regression and evaluated using receiver operating characteristic curves and five-fold cross-validation.

RESULTS

Independent predictive factors for good liquefaction included the absence of

diabetes [odds ratio (OR) = 0.339, P = 0.044], absence of pneumonia (OR = 0.218, P = 0.013), left-lobe abscess location (OR = 4.293, P = 0.041), cystic features (OR = 5.104, P = 0.025), and elevated preoperative serum alanine aminotransferase (ALT) levels (OR = 1.013, P = 0.041). The logistic regression model based on these factors demonstrated an area under the curve of 0.814, with a sensitivity of 90.24% and specificity of 67.86%. Five-fold cross-validation yielded an average accuracy of 83.61% and a kappa coefficient of 0.5209.

CONCLUSION

Pneumonia, diabetes, abscess location, abscess composition, and preoperative serum ALT levels are significant predictors of liver abscess liquefaction. The model can guide clinical decision-making.

Key Words: Pyogenic liver abscess; Percutaneous catheter drainage; Pneumonia; Diabetes; Computed tomography

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Core Tip: This study identifies key clinical, laboratory, and imaging factors associated with the degree of liquefaction in pyogenic liver abscesses. A predictive model was developed based on these factors to assess the degree of liquefaction, providing valuable guidance for optimizing the timing of clinical aspiration and drainage, thereby improving patient outcomes.

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INTRODUCTION

Pyogenic liver abscess (PLA) is a severe abdominal infectious disease. Although the incidence of PLA in the general population is relatively low and varies across different regions worldwide, its incidence has been rising steadily in recent years in many regions[1-4]. Currently, the combination of antibiotics and percutaneous catheter drainage (PCD) has become the first-line treatment for uncomplicated PLA, while surgical intervention is now reserved for cases where interventional treatment fails or is unsuitable due to specific clinical conditions[5,6]. Currently, the combination of antibiotics and PCD has become the first-line treatment for uncomplicated PLA, while surgical intervention is now reserved for cases where interventional treatment fails or is unsuitable due to specific clinical conditions[7-9]. Additionally, studies suggest that poorly liquefied abscesses might benefit more from conservative treatment, as drainage of these lesions often provides little or no benefit[10]. Conversely, if a well-liquefied abscess is not timely drained, the patient's condition may worsen, adversely affecting prognosis and potentially leading to life-threatening complications [11]. In clinical practice, discrepancies often arise between imaging findings and actual drainage outcomes. For example, some abscesses appearing well-liquefied on ultrasound (US) or computed tomography (CT) produce less than 5 mL of drainage fluid within 24 hours post-PCD, or even none. Conversely, some abscesses that appear poorly liquefied on US or CT exhibit unexpectedly high drainage volumes. This highlights the limitations of relying solely on empirical judgment to assess abscess liquefaction, which may result in mistimed drainage procedures and compromise patient outcomes. Despite its clinical importance, research on factors affecting PLA liquefaction remains limited[12,13]. Therefore, it is necessary to further investigate the factors influencing the liquefaction of liver abscesses to optimize clinical decision-making and improve patient outcomes.

Although the liquefaction degree of PLA plays a critical role in determining the optimal timing for percutaneous drainage, research on the factors influencing liquefaction remains limited. Moreover, no reliable models or standardized criteria currently exist to accurately assess the liquefaction status of abscesses. To address this research gap, this study focuses on patients undergoing PCD, systematically analyzing the relationships between postoperative drainage volume, clinical characteristics, CT imaging features, and laboratory indicators. We aim to identify key predictive factors of liquefaction, providing a scientific basis for optimizing clinical decision-making and improving patient outcomes.

MATERIALS AND METHODS

Study population

Given that this study adopts a retrospective design, the ethics committee approved a waiver of written informed consent.

We identified patients coded asDB90.0 under the 11th revision of the International Classification of Diseases in the hospital database between January 2017 and February 2023. To control for potential variability in abscess drainage volume caused by differences in surgical techniques among operators, only patients whose procedures were performed

by the same surgeon were included. The exclusion criteria were as follows: (1) Patients who did not undergo PCD or had more than one drainage catheter placed during PCD; (2) Patients whose drain age catheter dislodged within 24 hours post-PCD, either spontaneously or due to external factors; (3) Patients without recorded drainage volume within 24 hours post-PCD; (4) Patients with drainage catheter blockage within 24 hours post-PCD; (5) Patients with missing imaging or laboratory data within 24 hours preoperatively; and (6) Patients with multiple abscesses. A total of 110 patients met the inclusion criteria and were enrolled in the study.

Patient grouping

Currently, standardized quantitative criteria for differentiating between well-liquefied and poorly liquefied liver abscesses in the context of PCD are lacking. To address this, we established a pragmatic classification system based on the ratio of postoperative 24-hour drain age volume to the initial abscess volume (as determined by pre-procedural imaging). The cutoff value of 0.3 was selected primarily based on our clinical experience, as well as the practical challenges encountered during PCD, especially in cases of poorly liquefied abscesses. The rationale for recording the 24-hour postoperative drainage volume is that, under normal circumstances, the fluid within the abscess cavity is typically drained within 24 hours. Any additional fluid beyond this timeframe is primarily due to further necrosis of inflammatory cells or liver tissue. Specifically, our clinical observations indicated that when the ratio fell below 0.3, securing the drainage catheter became significantly more challenging. This difficulty in catheter fixation directly resulted in a considerably higher rate of catheter dislodgement, thus compromising both the efficacy of drainage and patient safety. Conversely, while a higher ratio could ensure a lower catheter dislodgement rate, it could also lead to missing the optimal drainage timing for some patients, consequently impacting their prognosis. Based on these considerations, we ultimately determined that 0.3 was the most appropriate cutoff value. This resulted in 82 patients being classified into the well-liquefied group and 28 into the poorly liquefied group.

Methods

The laboratory test data and demographic characteristics, including age, gender, BMI, preoperative clinical manifestations, laboratory test data within 24 hours before surgery, and postoperative 24-hour drainage volume, were all obtained from the hospital database. Abdominal CT scans performed within 24 hours prior to PCD were collected for the patients.

CT scan image processing and delineation

All patients underwent preoperative CT or contrast-enhanced CT (CECT) scans. However, only plain CT images (with a slice thickness of 1 mm) were used for contouring and software calculations. We did not utilize CECT images primarily because, in clinical practice, plain CT is considered superior for assessing the liquefaction degree of liver abscesses. The use of contrast agents increases the CT values of blood vessels and the normal liver tissue surrounding the lesions. Due to the "partial volume effect", this can lead to the enhancement of CT values in certain parts of the lesions, thereby affecting the evaluation of lesion size and liquefaction. CECT is mainly used to differentiate liver abscesses from other diseases when the diagnosis is uncertain[14,15]. Some studies have also suggested that CECT is not entirely accurate in determining the liquefaction and necrosis of abscesses[16,17].

Before presenting the images to two radiologists with over ten years of experience, all patient-related information was removed. Discrepancies in image interpretation and region of interest (ROI) delineation between the two radiologists were resolved through consensus. In this study, the liquefied liver abscess features determined jointly by the two radiologists included: (1) The location of the abscess; and (2) The presence of gas. The delineated ROIs were then reconstructed in three dimensions, and the following characteristics of the liver abscess were calculated using software (three dimensional Slicer): (1) Lesion volume; (2) Maximum cross-sectional length of the lesion; (3) Maximum three-dimensional length of the lesion; (4) Mean CT value of the lesion; (5) Presence of solid components in the lesion (defined as components with CT values ≥ 20 HU accounting for more than 50% of the lesion); (6) 10^{th} percentile and 90^{th} percentile CT attenuation values (to minimize the influence of gas, hemorrhage, and calcification within the lesion on CT attenuation values); and (7) The attenuation range between the 10^{th} and 90^{th} percentiles.

Statistical analysis

Categorical data were expressed as *n* (%) and analyzed using the χ^2 test. For continuous data, normality testing revealed that most variables did not conform to a normal distribution. To ensure consistent analysis methods, all continuous data were described using medians and interquartile ranges. Comparisons between two groups were performed using the Mann-Whitney *U* test. In multivariate analysis, variables identified as significant in univariate analysis ($P \leq 0.05$) were included, and the final regression model was developed using a stepwise selection method. A diagnostic model was established based on the beta coefficients of the logistic regression model. The model's performance was assessed using the receiver operating characteristic curve. A five-fold cross-validation method was employed to evaluate the model's efficacy. This study utilized three-dimensional Slicer (version 5.6.2), statistical product and service solutions (version 25.0, IBM Co., Armonk, NY, United States), R (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism (version 10.1.2, GraphPad Software, San Diego, CA, United States) for image processing, statistical analyses, and data visualization.

RESULTS

A total of 110 patients who underwent PCD were included in this study and categorized into the well-liquefied group (82 patients) and the poorly liquefied group (28 patients) on the basis of their treatment outcomes; thus, the prevalence of poor liquefaction was 25.45%. Table 1 shows the clinical and laboratory characteristics of the two groups and the results of their statistical comparisons. There were no significant differences in demographic parameters or certain comorbidities (*e.g.*, malignancy and hypertension) between the groups. Notably, the prevalence of diabetes in the well-liquefied group was 46.3%, which was significantly lower than the 71.4% reported in the poorly liquefied group (P = 0.022). Similarly, the prevalence of pneumonia was markedly lower in the well-liquefied group (12.2%) than in the poorly liquefied group (39.3%, P = 0.002). Additionally, the serum alanine transaminase (ALT) level was significantly greater in the well-liquefied group (P = 0.041). Although no patients with impaired consciousness were observed in the poorly liquefied group, the difference with the well-liquified group was not statistically significant (P = 0.057). Further multivariable analysis revealed that diabetes [odds ratio (OR) = 0.338, 95% confidence interval (CI): 0.118-0.971, P = 0.044] and pneumonia (OR = 0.213, 95%CI: 0.059-0.764, P = 0.018) were independent predictors of poor liquefaction. The serum ALT level (OR = 1.013, 95%CI: 1.001-1.025, P = 0.041) was also significantly associated with the liquefaction outcome.

Table 2 compares the CT characteristics of the patients in the two groups. Univariable analysis revealed that the lesion volume in the well-liquefied group was significantly smaller than that in the poorly liquefied group [median values: 88.48 cm³ (37.68, 164.03) *vs* 110.45 cm³ (89.16, 207.13), P = 0.035]. Additionally, the proportion of abscesses located in the left lobe was significantly greater in the well-liquefied group (61.0%) than in the poorly liquefied group (10.7%, P = 0.005), as was the occurrence of cystic features (34.1% *vs* 10.7%, P = 0.017). There were no significant differences between the two groups regarding the mean CT values, median CT values, or other imaging parameters. Multivariable logistic regression analysis revealed that abscess location in the left lobe (OR = 4.305, 95%CI: 1.065-17.404, P = 0.041) and the occurrence of cystic features (OR = 5.037, 95%CI: 1.187-21.378, P = 0.028) were independent predictors of good liquefaction. However, lesion volume was not significantly associated with patient outcomes (P = 0.919).

Multivariable logistic regression analysis was conducted again using the statistically significant factors identified in the previous analyses, including diabetes, pneumonia, serum ALT levels, abscess location, and abscess composition (Figure 1). The results revealed that pneumonia (OR = 0.218, 95%CI: 0.065-0.727, P = 0.013) and diabetes (OR = 0.339, 95%CI: 0.118-0.973, P = 0.044) were protective factors against good liquefaction, whereas the presence of cystic features (OR = 5.104, 95%CI: 1.229-21.196, P = 0.025), abscess location in the left lobe (OR = 4.293, 95%CI: 1.065-17.305, P = 0.041), and elevated preoperative serum ALT levels (OR = 1.013, 95%CI: 1.001-1.025, P = 0.041) were predictive of good liquefaction. The established logistic regression model was as follows: Logit (P) = 0.666 - 1.525A - 1.081B + 1.630C + 1.457D + 0.012E. Where A represents pneumonia (0 = no, 1 = yes), B represents diabetes (0 = no, 1 = yes), C represents cystic features (0 = no, 1 = yes), D represents abscess location (0 = right lobe, 1 = left lobe), and E represents preoperative ALT levels. The receiver operating characteristic curve of the diagnostic model is shown in Figure 2. The area under the curve was 0.814 (95%CI: 0.709-0.919). The maximum Youden index was 0.581, and the optimal cutoff value was 0.5485, yielding a sensitivity of 90.24% and a specificity of 67.86%. Fivefold cross-validation was performed to validate the model, yielding an average accuracy of 83.61% and an average kappa coefficient of 0.5209. Among the folds, the best performance was observed in fold 1, with an accuracy of 95.65% and a kappa coefficient of 0.8808, whereas the worst performance was in fold 5, with an accuracy of 73.91% and a kappa coefficient of 0.3235.

DISCUSSION

In this study, the incidence of good abscess liquefaction was 75.55%. Our findings indicate that pneumonia, diabetes, abscess location, and internal abscess composition are independent predictors of liquefaction degree. Additionally, serum ALT levels were significantly associated with good abscess liquefaction.

Our study suggests that pneumonia is indicative of poor liquefaction in liver abscesses, which we believe may be associated with *Klebsiella pneumoniae (K. pneumoniae)* as the predominant pathogen in pneumonia-related PLA patients. Liver abscesses caused by *K. pneumoniae* are typically characterized by poor liquefaction. Since its initial identification in Taiwan in the 1980s, *K. pneumoniae* has become an increasingly common pathogen, eventually replacing *Escherichia coli* as the primary causative agent of liver abscesses[18]. *K. pneumoniae* frequently exhibits extrahepatic migration to other tissues and organs, such as the lungs, brain, and eyes, leading to the development of invasive *K. pneumoniae* liver abscess syndrome (IKPLAS)[19]. As this is a retrospective study, we cannot determine the exact sequence of events between the occurrence of PLA and pneumonia. However, a study by Chung *et al*[20] indicated that the likelihood of developing pneumonia significantly increases after the onset of PLA, with *K. pneumoniae* accounting for 84.9% of the pathogens involved. Meanwhile, a study by Ho *et al*[21] mentioned that if a distant abscess develops shortly after the onset of pneumonia, the likelihood of *K. pneumoniae* being the causative pathogen significantly increases. We believe that regardless of the sequence of disease onset, once a PLA patient develops pneumonia, the likelihood of *K. pneumoniae* being the causative pathogen increases. Due to its high invasion, *K. pneumoniae* can rapidly damage the surrounding normal liver tissue, preventing some of the necrotic liver tissue within the abscess from having sufficient time to undergo liquefaction[11,22,23]. Additionally, certain *K. pneumoniae* serotypes, especially in East Asia, possess anti-phagocytic and anti-neutrophil properties, which allow for the preservation of some liver tissue within the abscess that has not yet undergone necrosis[24,25]. Under the combined effects of these factors, IKPLAS typically presents as poor liquefaction. However, since we only recorded the drainage volume from the abscess 24 hours post-surgery, the time frame may be insufficient for IKPLAS. Some *K. pneumoniae* strains have high viscosity, which can lead to obstruction of the drainage

Table 1 Clinical characteristics and laboratory indicators of patients, *n* (%)

Variables	PL (*n* = 28)	WL (*n* = 82)	Univariate analysis		Multivariate analysis	
			Z value	*P* value	*P* value	OR (95%CI)
Gender	19 (67.9)	51 (62.2)	-0.535	0.591		
Age (years), median (25^{th}, 75^{th} percentiles)	69.00 (62.00, 77.00)	68.00 (56.00, 73.00)	-0.563	0.574		
BMI, median (25^{th}, 75^{th} percentiles)	22.97 (20.82, 27.31)	22.69 (20.40, 26.15)	-0.161	0.872		
Malignancy	4 (14.3)	18 (22.0)	0.872	0.381		
Diabetes	20 (71.4)	38 (46.3)	-2.285	0.022[a]	0.044[a]	0.338 (0.118-0.971)
Hypertension	7 (25.0)	30 (27.6)	1.115	0.263		
Cholecystitis	3 (10.7)	12 (14.6)	0.519	0.602[1]		
Fever	20 (71.4)	56 (68.3)				
Pneumonia	11 (39.3)	10 (12.2)	-3.135	0.002[a]	0.018[a]	0.213 (0.059-0.764)
Consciousness disturbance	0 (0.0)	13 (15.9)	2.233	0.057[1]		
Respiratory dysfunction	1 (3.6)	14 (17.1)	1.789	0.139[1]		
Laboratory tests, median (25^{th}, 75^{th} percentiles)						
WBC ($\times 10^9$/L)	10.27 (8.58, 13.49)	11.45 (9.04, 14.21)	-0.650	0.948		
LYM (%)	10.90 (5.32, 16.18)	7.60 (4.62, 12.77)	-1.047	0.295		
HCT (%)	32.85 (28.95, 37.25)	32.10 (28.78, 36.40)	-1.161	0.246		
NP (%)	81.55 (75.35, 87.85)	84.30 (77.35, 88.90)	-1.060	0.289		
PLT ($\times 10^9$/L)	240.50 (162.25, 357.50)	212.00 (130.75, 287.50)	-0.419	0.676		
PT (seconds)	12.85 (12.10, 13.38)	13.35 (12.20, 14.03)	-1.644	0.100		
INR	1.12 (1.08, 1.18)	1.17 (1.07, 1.27)	-0.738	0.461		
TT (seconds)	15.75 (15.15, 17.28)	16.70 (15.60, 17.50)	-1.411	0.158		
Cr (μmol/L)	60.95 (54.05, 76.45)	62.50 (52.78, 85.25)	-1.215	0.224		
Urea (mmol/L)	5.18 (4.13, 5.91)	5.11 (3.72, 8.65)	-1.562	0.118		
TBIL (μmol/L)	17.25 (11.98, 25.98)	18.05 (13.30, 28.03)	-0.532	0.595		
ALT (U/L)	33.35 (21.45, 71.25)	49.90 (32.90, 95.50)	-2.350	0.019	0.041[a]	1.013 (1.001-1.025)
GGT (U/L)	119.00 (90.00, 204.75)	124.50 (62.75, 238.25)	-1.517	0.129		
FIB (g/L)	6.70 (5.58, 7.74)	6.40 (4.47, 7.49)	-1.379	0.168		
TP (g/L)	59.80 (54.55, 67.35)	60.60 (54.50, 65.10)	-0.546	0.585		
GLOB (g/L)	30.70 (27.53, 37.53)	31.55 (27.63, 36.60)	-0.384	0.701		
ALB (g/L)	28.35 (24.83, 31.50)	27.45 (24.78, 32.33)	-0.254	0.800		
A/G ratio	0.93 (0.78, 1.05)	0.90 (0.73, 1.05)	-0.620	0.951		

[a]$P < 0.05$.

[1]P calculated χ^2 exact test.

PL: Poor liquefaction; WL: Well liquefaction; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; WBC: White blood cell; LYM: Lymphocyte percentage; HCT: Hematocrit; NP: Neutrophil percentage; PLT: Platelet count; PT: Prothrombin time; INR: International normalized ratio; TT: Thrombin time; Cr: Creatinine; TBIL: Total bilirubin; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; FIB: Fibrinogen; TP: Total protein; GLOB: Globulin; ALB: Albumin; A/G ratio: Albumin/globulin ratio.

Table 2 Comparison of patient computed tomography characteristics, *n* (%)

CT features	PL (*n* = 28)	WL (*n* = 82)	Univariate analysis		Multivariate analysis	
			Z value	*P* value	*P* value	OR (95%CI)
Lesion volume (cm³), median (25th, 75th percentiles)	110.45 (89.16, 207.13)	88.48 (37.68, 164.03)	-2.107	0.035[a]	0.919	1.00 (1.00-1.00)
Mean CT value (HU), median (25th, 75th percentiles)	25.10 (19.93, 29.47)	23.04 (17.50, 27.19)	-1.496	0.135		
Median CT value (HU), median (25th, 75th percentiles)	26.00 (21.00, 29.75)	23.00 (19.00, 27.00)	-1.506	0.132		
10% CT value (HU), median (25th, 75th percentiles)	6.50 (-2.75, 10.75)	3.50 (-3.50, 10.00)	-0.666	0.505		
90% CT value (HU), median (25th, 75th percentiles)	44.00 (39.50, 49.75)	43.00 (38.00, 49.25)	-0.721	0.471		
CT value range (HU), median (25th, 75th percentiles)	38.50 (28.00, 51.00)	37.50 (29.75, 51.00)	-0.779	0.436		
Maximum cross-sectional diameter (cm), median (25th, 75th percentiles)	7.50 (6.57, 8.79)	7.23 (5.42, 9.31)	-1.118	0.263		
Maximum 3D diameter (cm), median (25th, 75th percentiles)	8.32 (7.46, 10.43)	8.23 (6.33, 10.41)	-0.837	0.403		
Abscess location (left lobe)	3 (10.7)	50 (61.0)	-2.764	0.005[a]	0.041[a]	4.305 (1.065-17.404)
Presence of gas	4 (14.3)	17 (20.3)	0.746	0.454		
Cystic appearance	3 (10.7)	28 (34.1)	2.369	0.017[a]	0.028[a]	5.037 (1.187-21.378)

[a]*P* < 0.05.

PL: Poor liquefaction; WL: Well liquefaction; OR: Odds ratio; CI: Confidence interval; CT: Computed tomography; HU: Hounsfield unit; 3D: Three dimensional.

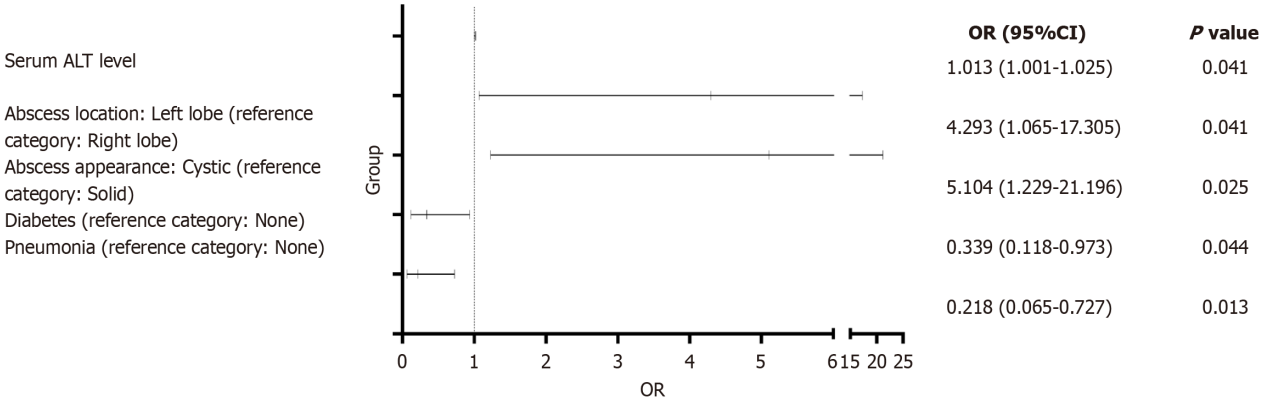


Figure 1 Multivariable analysis indicating good liquefaction. ALT: Alanine aminotransferase; OR: Odds ratio; CI: Confidence interval.

tube and a slower drainage process, potentially preventing complete drainage of the abscess within 24 hours[26-28].

Diabetes is an important independent risk factor for PLA, not only increasing the incidence of PLA but also having a negative impact on the prognosis of PLA patients[29,30]. In the multivariate analysis, the absence of diabetes was identified as an independent predictor of good abscess liquefaction. One important reason for this might be the compromised immunity in diabetic patients. Diabetes can lead to a reduction in dendritic cells, diminished chemotaxis and phagocytic activity of neutrophils, and impairment of neutrophil extracellular traps and macrophage phagocytosis [30-32]. Additionally, compared to non-diabetic individuals, diabetic patients tend to have more biofilm-associated bacteria within their lesions. The formation of this biofilm enables microorganisms to partially evade the immune surveillance system[31,33]. Moreover, due to the compromised immune system in diabetic patients, they tend to use more antibiotics compared to non-diabetic individuals. Some studies have found a gradual increase in antibiotic use among diabetic patients[34,35]. The increased use of antibiotics in diabetic patients may lead to a higher likelihood of drug-resistant bacteria within PLA lesions. This, in turn, makes them more resistant to conventional antibiotics[35,36]. Finally,

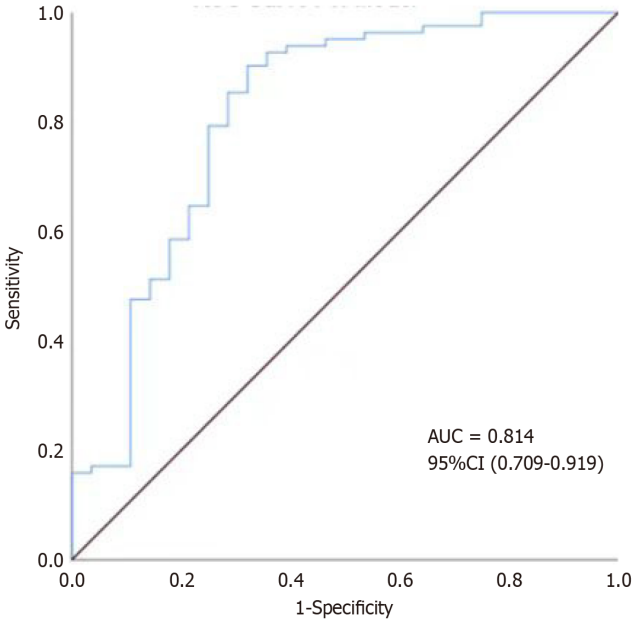


Figure 2 Receiver operating characteristic curve of the model. AUC: Area under the curve; CI: Confidence interval.

a study by Thurlow *et al*[37] revealed that the metabolic dysregulation caused by diabetes also affects the immune system's ability to eliminate infected hepatocytes to a certain extent. Under the combined influence of the aforementioned factors, the immune function within liver abscess lesions of diabetic patients is weakened, resulting in impaired clearance of necrotic tissue and inflammatory cells in the affected area. This limitation hinders the adequate formation of pus, ultimately leading to poor liquefaction.

Liver abscess, as a benign space-occupying lesion of the liver, can have a certain impact on liver function. Two isoforms of serum alanine aminotransferase, ALT1 and ALT2, are highly expressed in hepatic cells[38]. Hepatocyte necrosis leads to an increase in serum ALT levels, which is positively correlated with the degree of liver damage[39,40]. In well-liquefied lesions, most hepatocytes have already undergone necrosis, whereas in poorly liquefied lesions, most hepatocytes remain in the stage of leukocyte infiltration. As a result, well-liquefied abscesses release more ALT into the serum, leading to higher ALT levels compared to patients with poorly liquefied abscesses.

Lesions exhibiting cystic features can indicate well-liquefied abscesses, a result consistent with our clinical experience. Many interventional physicians currently use this factor to determine whether an abscess has liquefied well. Our study results show that in the poorly liquefied group, lesions predominantly presented with solid features, accounting for as much as 89.3%, while in the well-liquefied group, the proportion of solid features decreased to 65.9%. This suggests that lesion composition offers a high accuracy for identifying poorly liquefied lesions, but the accuracy for identifying well-liquefied lesions is relatively lower. Therefore, we believe it is necessary to consider other predictive factors to improve the overall accuracy in assessing abscess liquefaction.

Our study results found that abscesses located in the left lobe had a higher degree of liquefaction compared to those located in the right lobe, and this difference was statistically significant. This conclusion was somewhat unexpected, as some studies suggest that anatomical location does not affect the overall structure of the abscess[41,42]. We believe this difference may be due to the distinct pathogenic microbiota in the left and right lobes. Infection originating from gut microbiota *via* the portal vein is an important cause of PLA[43]. Since the right liver is heavier in mass and has larger bile duct volume and density compared to the left liver, blood flow from the mesentery primarily flows through the portal vein to the right lobe of the liver[44,45]. Therefore, the hemodynamic differences between the left and right lobes may lead to distinct microbial infection characteristics, which in turn affect the degree of liquefaction of the abscess.

Among the 28 patients with poor liquefaction, none showed signs of consciousness disturbance, while 13 patients (15.9%) in the good liquefaction group experienced consciousness disturbances. Although this result was not statistically significant in the univariate analysis (P = 0.057), it may be due to the insufficient sample size. We believe that with a larger sample size, this result could achieve statistical significance. This could also be attributed to the longer course of the lesions in the good liquefaction group compared to the poor liquefaction group. As a result, the pathogens (such as *K. pneumoniae*) in the lesions had more opportunities to enter the bloodstream, leading to extrahepatic infections.

This study explored the predictive factors associated with good liquefaction in pyogenic liver abscesses and developed a prediction model based on these factors. The model aims to provide scientific evidence for clinicians to optimize the timing of puncture, ensuring that patients receive puncture drainage and other therapeutic interventions at the optimal time. This approach is intended to improve the success rate of treatment, reduce the occurrence of complications, enhance patient prognosis, and provide important support for clinical decision-making.

All patients in this study underwent preoperative US examination. However, for some patients, the judgment of abscess liquefaction degree based on preoperative US did not align with the actual postoperative drainage outcomes (Figure 3). In this study, we did not use any US images for data analysis, primarily due to the following reasons: (1) US images are two-dimensional, and since this is a retrospective study, the stored images were insufficient for three-

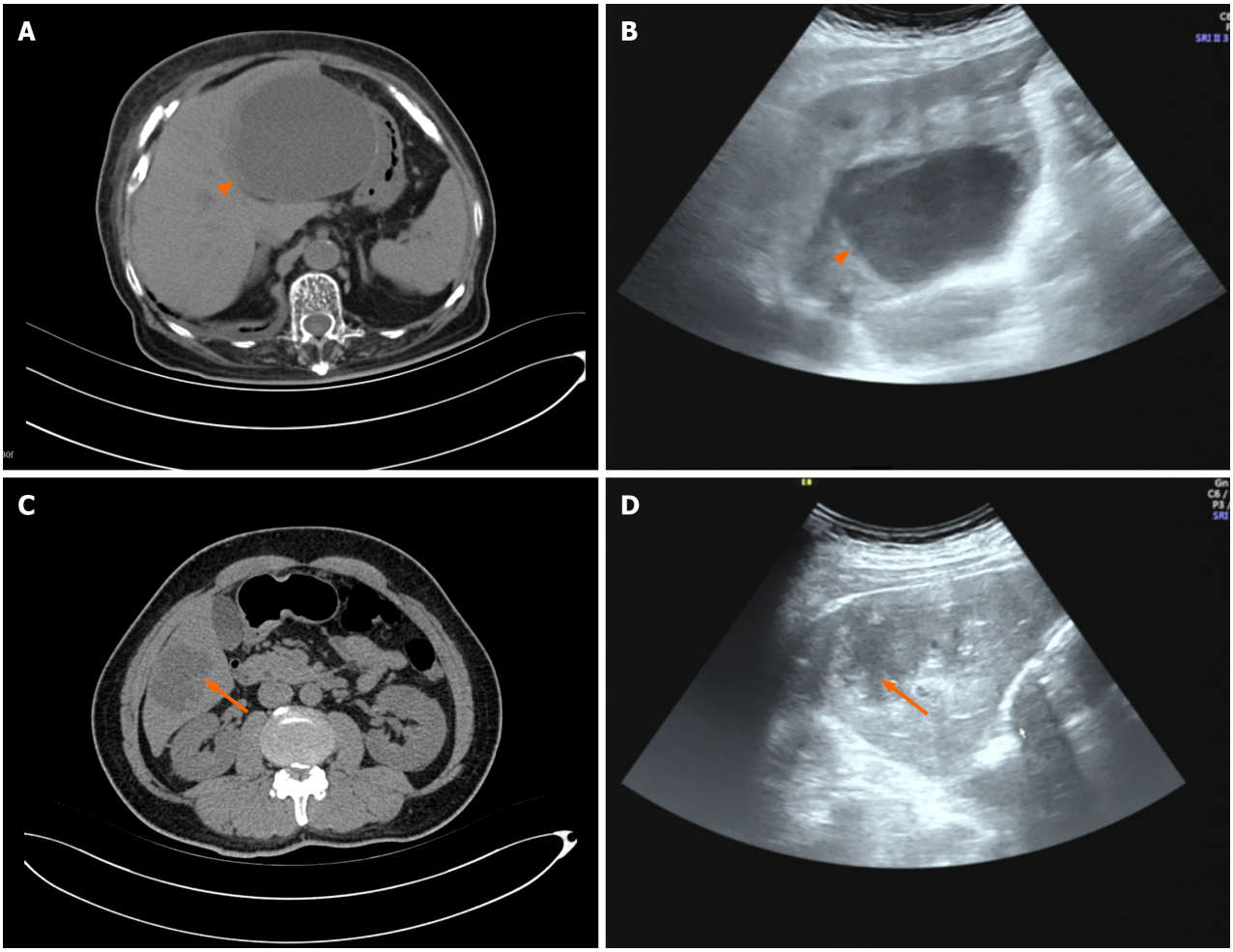


Figure 3 Elderly patients with diabetes and hypertension. A and B: An elderly female patient; Computed tomography (CT) scan (A); Ultrasound (US) examination (B). These results were interpreted by two radiologists as showing well-formed liquefaction. The postoperative drainage volume was only 100 mL, with a ratio of 0.23 compared to the lesion volume; C and D: An elderly male patient; CT scan (C); US examination (D). The degree of liquefaction of the lesion is less than in A and B, but the postoperative drainage volume was 61 mL, with a ratio of 0.85 compared to the lesion volume.

dimensional reconstruction of the lesions using software. In contrast, CT images provide similar data but are more accurate; and (2) The US examinations were performed by different operators, and variations in their operating habits, image recording practices, and machine parameter settings were significant, leading to larger data collection errors in US compared to CT.

Our study has several limitations that warrant discussion. First, as a retrospective, single-center study, the generalizability of our findings is inherently limited. The reliance on existing medical records, rather than standardized data collection, may have introduced bias or missing data, affecting the robustness of our conclusions. For instance, when assessing the influence of pneumonia and diabetes on abscess liquefaction, we hypothesized that differences between the liquefied and non-liquefied groups could, in part, be attributed to the predominance of *K. pneumoniae* in the diseased group. However, the lack of bacterial culture data for many patients prevented us from fully exploring this hypothesis. Additionally, most patients had comorbidities requiring multiple medications during treatment, which may have influenced abscess liquefaction, as suggested by prior research[46,47]. Lastly, the CT imaging data were obtained using different scanners with varying settings and parameters, which could have introduced subtle inconsistencies in CT values, potentially affecting the precision of our quantitative findings. To minimize such variability, future studies should adopt standardized imaging protocols.

CONCLUSION

This study analyzed the factors influencing the degree of liquefaction in hepatic abscesses and identified preoperative serum ALT levels, diabetes status, pneumonia status, abscess location, and cystic features as important predictors of liquefaction. The predictive model constructed based on these factors demonstrated good diagnostic performance, providing scientific evidence for clinicians to optimize the timing of puncture procedures. The occurrence of poor liquefaction is closely related to conditions such as diabetes and pneumonia, suggesting that the impact of underlying diseases on liquefaction should be considered during treatment. Future prospective, multi-center studies could further

validate the clinical utility of the model to improve treatment success rates and outcomes for hepatic abscess patients.

FOOTNOTES

Author contributions: Long HY was responsible for the conceptualization and design of the study, literature search, and drafting of the manuscript; Yan X was in charge of data collection, organization, and analysis; Meng JX performed the critical analysis of the study, participated in data organization, and revised the manuscript; Xie F supervised the study, provided significant guidance, and finalized the manuscript as the corresponding author; All authors have read and approved the final manuscript.

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Informed consent statement: This study is a retrospective study that exempts patients from informed consent.

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

Data sharing statement: Anonymized data not presented herein is available upon reasonable request from the corresponding author on rational request by any qualified researcher.

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ORIGINAL ARTICLE

Retrospective Study

Comparison of the efficacy of carbapenems and cephalosporins for postoperative treatment of perforated appendicitis in children

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Abstract

BACKGROUND

Pediatric perforated appendicitis (PPA) is a severe acute condition requiring surgical intervention and postoperative antibiotic therapy. Antibiotic selection differs significantly among pediatric centers, and an ideal postoperative anti-infective approach for PPA management has yet to be established.

AIM

To examine the spectrum of pathogenic bacteria in pediatric PPA and to summarize the postoperative experience with carbapenem (CBP) and cephalosporin (CPS) antibiotics.

METHODS

We retrospectively analyzed medical records of 65 children (43 boys, 22 girls; mean age 6.92 ± 3.41 years) with PPA who underwent surgery at our hospital between December 2019 and August 2022. Data were collected in September 2023. Based on postoperative antibiotic selection, patients were divided into CBP (32 cases) and CPS (33 cases) groups. Chi-square and T-tests compared recovery outcomes, while univariate and multivariate regression models identified inde-

pendent factors affecting postoperative recovery.

RESULTS

There were no significant differences between the two groups in gender, age, weight, height, body mass index, baseline ear temperature, or heart rate ($P > 0.05$). *Escherichia coli* (40.00%) and *Pseudomonas aeruginosa* (24.62%) were the most common pathogens in PPA. Postoperative analysis showed significantly shorter C-reactive protein (CRP) recovery times in the CPS group than in the CBP group [(6.18 ± 1.84) *vs* (8.12 ± 3.48) days, $P = 0.009$]. Univariate logistic regression indicated CPS selection (OR = 0.32, 95%CI: 0.10-0.97, $P = 0.044$) was significantly associated with a higher CRP recovery rate within 7 days. Multivariate analysis confirmed CPS selection (OR = 3.49, 95%CI: 1.19-10.24, $P = 0.023$) as an independent factor affecting CRP recovery within 7 days postoperatively.

CONCLUSION

The choice of CBP or CPS independently affects CRP recovery within 7 days. CBP offers no advantage over CPS in treating PPA, with CPS also demonstrating favorable clinical outcomes.

Key Words: Children; Perforated appendicitis; Pathogenic bacteria; Carbapenems; Cephalosporins

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Core Tip: In the management of pediatric perforated appendicitis (PPA) post-surgery, our retrospective study demonstrates that cephalosporins (CPS) are as effective as carbapenems in achieving favorable clinical outcomes. Notably, CPS use is associated with significantly faster C-reactive protein recovery within seven days, highlighting its potential as a preferred antibiotic choice. These findings support optimizing antibiotic selection to enhance postoperative recovery and mitigate the risks of antibiotic resistance in children treated for PPA.

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INTRODUCTION

Acute appendicitis is the most common pediatric surgical emergency globally. Perforated appendicitis (PA) accounts for approximately 30% of pediatric appendicitis cases, with incidence rates being higher in younger children[1,2]. In comparison with non-PA, PA markedly impacts postoperative outcomes, significantly increasing the risk of complications, including abdominal or pelvic abscesses, bowel obstruction, and wound infections, with rates reaching up to 39% [3,4]. Severe PA may result in acute peritonitis, which can lead to dehydration, sepsis, paralytic ileus, or even death[5]. As a critical condition, peritonitis necessitates emergency surgical intervention[6]. Early surgical management is essential for preventing disease progression and mitigating associated risks[7-9].

During the progression of pediatric PA (PPA), bacterial transmigration and invasive infections play pivotal roles in its development and severity. Studies have demonstrated a positive correlation between the severity of clinical manifestations and the detection of bacterial pathogens. As inflammation intensifies, the permeability of the appendiceal wall increases, allowing a greater number of bacterial species to infiltrate, ultimately leading to perforation. This increase in bacterial diversity is associated with a higher risk of complications[10]. Bacteria absorbed through the peritoneum and mesentery can enter systemic circulation, leading to sepsis, which severely compromises patient survival and can be life-threatening. This underscores the importance of analyzing bacterial profiles and antibiotic susceptibility in pediatric cases. Perioperative antibiotic prophylaxis and treatment are crucial in managing appendicitis, significantly improving patient outcomes[11]. Various antibiotic regimens have been evaluated, with differing guidelines addressing their use. Ceftriaxone combined with metronidazole and other anti-infective agents, or broad-spectrum antibiotics with metronidazole, has been widely studied[12,13]. The triple-drug regimen of ampicillin, gentamicin, and clindamycin or metronidazole remains prevalent in hospitals globally[14]. Recent studies have advocated single-agent therapies, such as carbapenems (CBP) or tazobactam/piperacillin, as alternatives to dual or triple regimens for PPA[15,16]. However, resistance to ceftriaxone, particularly by extended-spectrum β-lactamase-producing bacteria and pseudomonas strains, necessitates timely escalation to more effective agents, such as tazobactam/piperacillin, to enhance clinical outcomes and reduce hospitalization duration[17].

Currently, there are no standardized guidelines for antibiotic use in PPA management[18]. Significant uncertainties remain regarding optimal treatment, and the comparative efficacy of CBP and cephalosporins (CPS) have not been thoroughly investigated. Our findings revealed generally low resistance rates to CBP, such as meropenem and imipenem. Appendix pus culture results revealed that not all pathogenic strains are sensitive to CBP. CPSs, being the most commonly used antibiotics for appendicitis, raise the question of whether CBP offers superior efficacy in PPA treatment.

This study aimed to address this gap by comparing postoperative outcomes in pediatric PPA cases treated with either CBP or CPS.

MATERIALS AND METHODS

General materials

We retrospectively reviewed the medical records of 65 children (43 boys, 22 girls; mean age: 6.92 ± 3.41 years) diagnosed with PPA and treated with standard laparoscopic appendectomy at our hospital's Pediatric Surgery Department between December 2019 and August 2022. We accessed these data in September 2023 using the hospital's Electronic Data Capture system for research. The antibiotic sensitivity of the pus samples collected from the surface of the appendix was recorded. A retrospective analysis was conducted on pediatric cases of physical activity in our hospital over the past 3 years, focusing on the clinical application of postoperative antibiotics and the duration of clinical follow-up observation (from the initial administration of antibiotics postoperatively until the children were discharged). The clinical outcomes of patients managed with CBP (32 cases) and CPS (33 cases) after PPA surgery were evaluated and compared.

Inclusion and exclusion criteria

Inclusion criteria: (1) The study will include data from November 2019 to August 2022; (2) The patient was diagnosed with PPA during surgery; (3) All patients underwent the traditional three-hole laparoscopic appendectomy and intraoperative procedures were performed according to the description of surgical methods; and (4) All children were treated with antibiotics postoperatively, either CBP or CPS, and were administered a single antibiotic until meeting the cessation criteria.

Exclusion criteria: (1) Cases outside the time frame; (2) Non-PA diagnosed during surgery; (3) Patients underwent either non-three-hole laparoscopic appendectomy or laparoscopic conversion to laparotomy; (4) Patients did not receive intraoperative abdominal irrigation or abdominal drainage tube; and (5) Postoperative antibiotics other than CBP or CPS were selected, or combination of antibiotics, or change of antibiotics.

Surgical methods

Three hole laparoscopic appendectomy was performed. The patients were placed in a Trendelenburg position angled 15° toward the surgeon. A 30-degree 5-mm camera was inserted through the umbilical trocar, and a 5-mm trocar was inserted through the McGilliard point and the suprapubic region. Throughout the surgical procedure, the appendix was excised entirely, the abdominal cavity was irrigated with normal saline, and drainage tubes were inserted into each abdominal cavity.

Strategy for antibiotic selection

For the CPS group, if antimicrobial susceptibility testing confirmed sensitivity or yielded inconclusive results for the initial CPS, the original regimen was maintained. If resistance was detected, a sensitive CPS alternative was selected. The initial CPS therapy was continued when the susceptibility results were negative but the clinical symptoms and laboratory findings showed improvement. Importantly, even in cases of resistance to CPS, symptomatic improvement was observed during treatment. Postoperative antibiotic discontinuation was based on the following criteria: (1) Tolerance of a normal diet with spontaneous bowel movements; (2) Absence of fever (ear temperature < 37.3 °C) for more than 48 hours; (3) Full resolution of abdominal symptoms, such as pain, bloating, diarrhea, or constipation; (4) No evidence of infection at the surgical site; and (5) C-reactive protein (CRP) levels < 10 mg/L (Figure 1).

Statistical analysis

Data analysis was conducted using GraphPad Prism 9.0. Continuous data with normal distribution were expressed as mean ± SD and analyzed using the *t* test. Categorical data were expressed as frequency (proportion) and analyzed using the χ^2 test. Univariate and multivariate analyses were performed using the binary/multinomial logistic regression model to evaluate the impact of perioperative factors on postoperative recovery. The OR and 95%CI were calculated to assess the impact of each factor on prognosis. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

RESULTS

General characteristics

There were no statistically significant differences in gender, age, weight, height, body mass index, ear temperature, or heart rate at baseline between the two groups ($P > 0.05$), confirming the comparability of the data (Table 1).

Analysis of the situation regarding pathogenic bacterial infections

A total of 65 samples were tested, all yielding positive bacterial cultures. Among these, 26 cases (40.00%) involved *Escherichia coli* (*E. coli*), 16 cases (24.62%) *Pseudomonas aeruginosa* (*P. aeruginosa*), 11 cases (16.92%) were co-infected with

Table 1 Preoperative baseline data characteristics of the two groups of patients, mean ± SD

Characteristics	CBP	CPS	*T* value or χ^2	*P* value
Number of patients (*n*)	32	33	-	-
Gender (*n*, male:female)	23:9	20:13	0.921	0.337
Age (year)	6.94 ± 3.48	6.86 ± 3.20	0.095	0.924
Weight (kg)	29.63 ± 15.64	24.26 ± 9.21	1.694	0.095
Height (m)	1.21 ± 0.23	1.25 ± 0.23	0.747	0.457
BMI (*n*)	18.48 ± 2.72	17.33 ± 2.77	1.829	0.071
Ear temperature (°C)[1]	37.92 ± 0.73	37.60 ± 0.716	1.735	0.088
Heart rate (bpm)	113.03 ± 16.53	111.12 ± 15.32	0.483	0.630

[1]Temperature measured on admission.
CBP: Carbapenem; CPS: Cephalosporin; BMI: Body mass index.

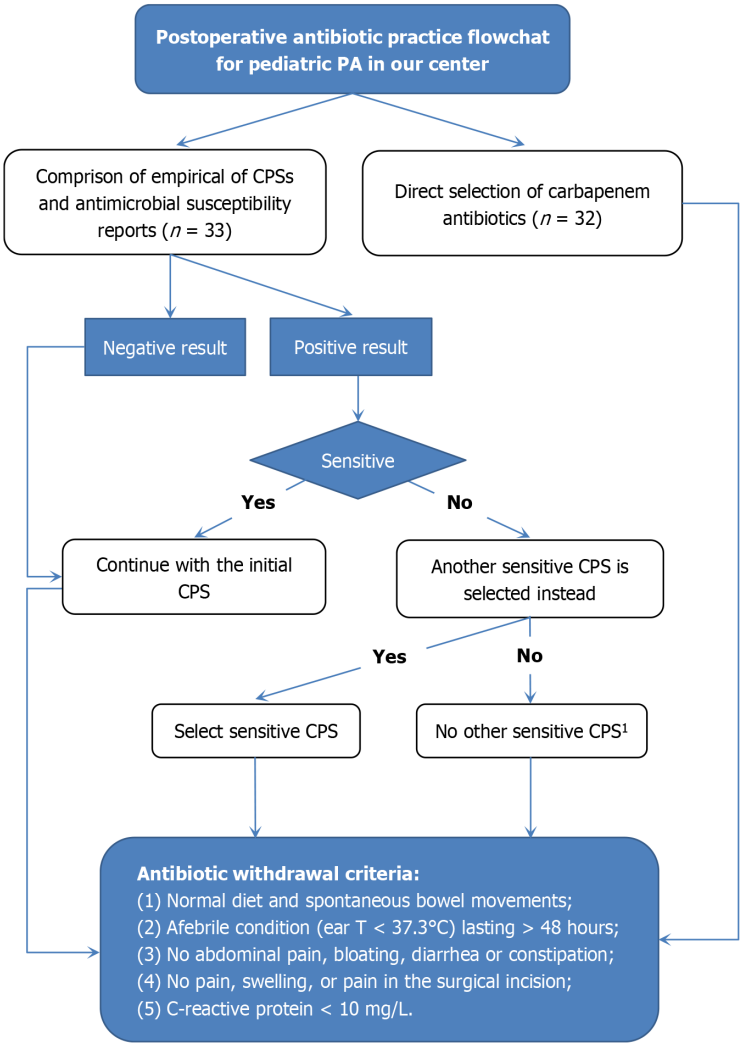


Figure 1 Postoperative antibiotic management flowchart for pediatric perforated appendicitis in our center. [1]The detected strains were insensitive to other cephalosporin (CPSs), and the initial CPS was maintained until clinical symptoms and laboratory indicators improved. CPS: Cephalosporin; PA: Perforated appendicitis.

both bacteria, and 12 cases (18.46%) were caused by other strains, including *Klebsiella pneumoniae*, *Proteus vulgaris*, *Streptococcus constellatus*, *Comamonas testosteroni*, *Citrobacter freundii*, *Enterococcus avium*, and *Streptococcus anginosus*. The predominant pathogens in PPA were *E. coli* and *P. aeruginosa*. Both strains exhibited 0.00% resistance to ceftazidime, piperacillin-tazobactam, and CBP, whereas *P. aeruginosa* also showed 0.00% resistance to aztreonam and ceftazidime. Mixed infections involving two strains were labeled as "Combine" in the table, whereas other infections were categorized as "Others". Both categories displayed 0.00% resistance to amikacin, piperacillin-tazobactam, and CBP. For "Others", the highest resistance rate was observed with cefazolin at 75.00% (Table 2).

Impact of antibiotics on postoperative recovery

Postoperative characteristics revealed significantly shorter CRP recovery times in the CPS group compared with the CBP group [CPS: (6.18 ± 1.84) days *vs* CBP: (8.12 ± 3.48) days, $P = 0.009$]. However, the comparison of antibiotic effects on postoperative recovery showed no statistically significant differences between the two groups in gastrointestinal function (GF) recovery time, hospital stay length, or complications such as bowel obstruction, ascites, abdominal abscess, and wound infections (all $P > 0.05$) (Table 3).

Univariate analysis of binary logistic regression model to evaluate the impact of perioperative factors on postoperative recovery

Univariate analysis of baseline characteristics and C-reactive protein recovery rate within 7 days postoperatively: Among baseline characteristics, the proportion of CPS antibiotic selection (OR = 0.32, 95%CI: 0.10-0.97, $P = 0.044$) was significantly associated with a higher CRP recovery rate within 7 days postoperatively ($P < 0.05$) (Table 4).

Univariate analysis of baseline characteristics and gastrointestinal function recovery rate within 48 hours postoperatively: Among baseline characteristics, including gender, age, Ear temperature, antibiotic selection, and complications, none were significantly associated with a higher GF recovery rate within 48h postoperatively (all $P > 0.05$) (Table 5).

Multivariate analysis of perioperative characteristics and C-reactive protein recovery rate within 7 days postoperatively

Variables with $P < 0.05$ from the multivariate analysis of antibiotic selection was included in the multinomial logistic regression model. The results showed that antibiotic selection (OR = 3.49, 95%CI: 1.19-10.24, $P = 0.023$) was an independent factor affecting the CRP recovery rate within 7 days postoperatively (Table 6).

DISCUSSION

Newman *et al*[19] documented appendicitis perforation rates ranging from 20% to 76% across 30 pediatric hospitals in the United States, with an average of 36%. Acute PA is a frequent complication in pediatric appendicitis owing to anatomical and physiological factors, such as the free cecum, A thin appendix wall abundant in lymphoid tissue, common retinal dysplasia, and the extensive surface area of the peritoneal cavity. These factors increase the risk of PA, resulting in celiac inflammation, challenges in infection control, and elevated complication rates[20]. In the present study, Frequent postoperative complications included bowel obstruction [CBP: 3 cases (9.38%) *vs* CPS: 1 case (3.03%); $P = 0.287$], ascites [CBP: 3 cases (9.38%) *vs* CPS: 0 cases (0.00%); $P = 0.072$], abdominal abscess [CBP: 1 case (3.13%) *vs* CPS: 0 cases (0.00%); $P = 0.306$], and wound infections [CBP: 1 case (3.13%) *vs* CPS: 0 cases (0.00%); $P = 0.321$]. The rates of postoperative complications did not differ between the CBP and CPS groups. Some researchers have proposed omitting intraoperative pus cultures and antimicrobial susceptibility testing[21]. However, we argue that peritoneal pus culture remains cost-effective, convenient, and clinically valuable. Schülin *et al*[22] demonstrated considerable diversity in the appendix microbiome of acute pediatric appendicitis exhibits considerable diversity, with notable variations in microbial composition within the appendix lumen based on inflammation severity. These variations may contribute to the proliferation of pathogenic bacteria described in the appendix. In our study, pus cultures revealed common infections with *E. coli* and *P.* , with 26 cases (40.00%) involving *E. coli*, 16 cases (24.62%) involving *P. aeruginosa*, 11 cases (16.92%) involving both bacteria, and 12 cases (18.46%) caused by other strains, including *Klebsiella pneumonia*, *Proteus vulgaris*, *Streptococcus constellatus*, *Comamonas testosteroni*, *Citrobacter freundii*, *Enterococcus avium* and *Streptococcus anginosus*.

Antibiotics are crucial for the management of PPA. Tsai *et al*[23] highlighted that surgery is the optimal early treatment for PPA, thereby reducing both the antibiotic duration and hospital stay. According to Turel *et al*[24], selecting antibiotics based on pathogen test results is essential for guiding clinical PPA treatment. In our study, postoperative CRP recovery times were notably shorter in the CPS group than in the CBP group [CPS: (6.18 ± 1.84) days *vs* CBP: (8.12 ± 3.48) days, $P = 0.009$]. However, standardized protocols for postoperative antibiotic use in pediatric appendicitis remain unavailable[25]. The misuse of antibiotics has intensified the emergence of resistant bacterial strains, thereby diminishing the efficacy of conventional treatments. Plattner *et al*[26] concluded that in non-critical pediatric cases, broad-spectrum antibiotics or prolonged post-discharge antibiotic use did not significantly enhance clinical outcomes. Thus, the identification of the most effective antibiotic regimens is an ongoing research.

E. coli and *P. aeruginosa* exhibited high sensitivity to third-generation CPSs, such as ceftazidime and ceftizoxime, making these antibiotics suitable empirical agents for treating PPA while awaiting susceptibility results. Our findings indicate that certain bacteria are sensitive to CBP, but resistant to CPS. Although current guidelines exclude CBP as a first-line treatment for PPA, our results suggest its potential utility. Some studies have proposed management strategies

Table 2 Antimicrobial resistance profiles of the two major strains of bacteria, *n* (%)

Antimicrobial resistance	Pathogenic bacterial species			
	E. coli (*n* = 26)	*P. aeruginosa* (*n* = 16)	Combine (*n* = 11)	Others (*n* = 12)
Amikacin	1 (3.70)	0 (0.00)	0 (0.00)	0 (0.00)
Amoxicillin/clavulanic acid potassium	8 (30.77)	6 (37.50)	3 (27.27)	4 (33.33)
Aztreonam	4 (15.38)	0 (0.00)	0 (0.00)	1 (8.33)
Gentamicin	4 (15.38)	4 (25.00)	3 (27.27)	3 (25.00)
Ceftazidime	0 (0.00)	0 (0.00)	0 (0.00)	1 (8.33)
Cefuroxime	12 (46.15)	6 (37.50)	4 (36.36)	6 (50.00)
Cefazolin	15 (57.69)	9 (56.25)	5 (45.45)	9 (75.00)
SMZ-TMP	11 (42.31)	8 (50.00)	5 (45.45)	6 (50.00)
Piperacillin tazobactam	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Meropenem	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Imipenem	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Levofloxacin	3 (11.54)	2 (12.50)	2 (18.18)	0 (0.00)

E. coli: Escherichia coli; P. aeruginosa: *Pseudomonas aeruginosa.*

Table 3 Comparison of the effect of antibiotics on the postoperative recovery of children in two groups, *n* (%)

Project	CBP	CPS	*Z* value or χ^2	*P* value
CRP recovery time (days)	8.12 ± 3.48	6.18 ± 1.84	2.59	0.009
GF recovery time (hours)	38.84 ± 23.37	35.08 ± 20.92	0.61	0.542
Hospital stay length (days)	8.63 ± 3.01	8.97 ± 2.80	0.94	0.344
Complications			3.41	0.065
No	25 (78.12)	31 (93.94)		
Yes	7 (21.88)	2 (6.06)		
Bowel obstruction			1.13	0.287
No	29 (90.62)	32 (96.97)		
Yes	3 (9.38)	1 (3.03)		
Ascites			3.24	0.072
No	29 (90.62)	33 (100.00)		
Yes	3 (9.38)	0 (0.00)		
Abdominal abscess			1.05	0.306
No	31(96.87)	33 (100.00)		
Yes	1 (3.13)	0 (0.00)		
Wound infections			0.98	0.321
No	32 (100.00)	32 (96.97)		
Yes	0 (0.00)	1 (3.03)		

CRP: C-reactive protein; GF: Gastrointestinal function; CBP: Carbapenem; CPS: Cephalosporin.

Table 4 Univariate analysis of binary logistic regression model for baseline characteristics and C-reactive protein recovery rate within 7 days postoperatively, *n* (%)

Project	*n* = 65	OR	95%CI	*P* value
Gender				
Female	22 (33.85)	1.00	Refer	
Male	43 (66.15)	1.10	0.35-3.46	0.878
Age (year)				
≤ 5	24 (36.92)	1.00	Refer	
> 5	41 (63.08)	0.56	0.19-1.68	0.300
Ear temperature (°C)				
< 37.3	20 (30.77)	1.00	Refer	
≥ 37.3	45 (69.23)	0.61	0.19-1.99	0.415
Antibiotic selection				
CBP	32 (49.23)	1.00	Refer	
CPS	35 (53.85)	3.92	1.32-11.62	0.014
Complications				
No	56 (86.15)	1.00	Refer	-
Yes	9 (13.85)	0.82	0.18-3.71	0.797

CBP: Carbapenem; CPS: Cephalosporin.

Table 5 Univariate analysis of binary logistic regression model for baseline characteristics and gastrointestinal function recovery rate within 48 hours postoperatively, *n* (%)

Project	*n* = 65	OR	95%CI	*P* value
Gender				
Female	22 (33.85)	1.00	Refer	
Male	43 (66.15)	1.61	0.48-5.46	0.441
Age (year)				
≤ 5	24 (36.92)	1.00	Refer	
> 5	41 (63.08)	1.16	0.36-3.72	0.803
Ear temperature (°C)				
< 37.3	20 (30.77)	1.00	Refer	
≥ 37.3	45 (69.23)	0.32	0.08-1.35	0.122
Antibiotic selection				
CBP	32 (49.23)	1.00	Refer	
CPS	35 (53.85)	2.69	0.82-8.81	0.103
Complications				
No	56 (86.15)	1.00	Refer	-
Yes	9 (13.85)	0.819	0.17-4.01	0.806

CBP: Carbapenem; CPS: Cephalosporin.

Table 6 Multivariate analysis of multinomial logistic regression model for perioperative characteristics and C-reactive protein recovery rate within 7 days postoperatively, *n* (%)

Project	*n* = 65	OR	95%CI	*P* value
Antibiotic selection				
CBP	32 (49.23)	1.00	Refer	
CPS	35 (53.85)	3.49	1.19-10.24	0.023
Pathogenic bacteria species				
E. coli	26 (40.00)	1.00	Refer	
P. aeruginosa	16 (24.62)	0.84	0.20-3.56	0.818
Combine	11 (16.92)	0.76	0.15-3.89	0.739
Others	12 (20.00)	0.79	0.14-4.37	0.785

CBP: Carbapenem; CPS: Cephalosporin; *E. coli: Escherichia coli; P. aeruginosa*: *Pseudomonas aeruginosa.*

for CBP use[27]. However, The dependence on broad-spectrum antibiotics and the use of restricted-grade antibiotics heightens the risk of colonization and infection by multidrug-resistant organisms[28]. Notably, excessive empirical use of meropenem has been linked to the emergence of CBP-resistant gram-negative bacteria[29], necessitating cautious use. In our study, pathogens were largely sensitive to CPSs, penicillins, and aminoglycosides, making these drugs preferred for empirical therapy. Nonetheless, resistance of *E. coli* to penicillins, such as amoxicillin-clavulanic acid, has been associated with higher postoperative complication rates[30].

Aminoglycosides exhibit efficacy against both bacilli and *P. aeruginosa*, their nephrotoxic[31] and ototoxic[32] effects pose risks, particularly in pediatric patients. As a result, we prioritized CPSs as the primary antibiotics in our treatment protocol and research focus, avoiding aminoglycosides due to their potential adverse effects.

White blood cells (WBC) are key inflammatory cells, and their exudate plays a crucial role in the inflammatory response. However, WBC counts can fluctuate within a specific range depending on the time and functional state of the body. Additionally, some laboratory indicators may vary due to these factors, WBC are central to inflammatory processes, and their presence in exudates serves as a hallmark of inflammation. However, WBC counts fluctuate within a specific range depending on temporal, physiological, and functional states. Factors such as age, emotional stress, and pain can significantly influence WBC counts. Notably, in certain cases of severe infections, WBC counts may decrease rather than increase, limiting their specificity in assessing the severity of acute appendicitis[33]. Consequently, WBC counts were excluded from the withdrawal criteria. In contrast, CRP is widely recognized as one of the most sensitive biomarkers of acute-phase reactions in humans. CRP levels increase swiftly during acute inflammatory events and are largely unaffected by physiological factors or antibiotic therapy, showing a strong positive correlation with the severity of infection. Previous studies have reported that elevated CRP levels are significantly associated with the severity of appendicitis in pediatric patients, particularly in complicated PPA[34]. To eliminate potential bias in the definition of PA [35], we adopted a clear intraoperative definition and confined the study population to a narrowly defined group.

PPA predisposes patients, particularly children with compromised immune barrier function, to systemic infections, such as bacteremia and sepsis, necessitating combination antibiotic therapies or escalated treatment regimens. To minimize confounding variables, the study was restricted to pediatric patients without immunodeficiencies or hemodynamic instability. This approach reduced the influence of factors such as WBC count, peritoneal contamination, and operative duration, thereby enhancing the objectivity and precision of the study conclusions. Consequently, CRP was included as a key parameter for comparative evaluation. Our findings revealed that CRP recovery times were significantly shorter in the CPS group than in the CBP group [CPS: (6.18 ± 1.84) days *vs* CBP: (8.12 ± 3.48) days, $P = 0.009$]. The choice of CPS or CBP antibiotics was an independent determinant of CRP recovery rates within 7 days postoperatively (OR = 3.49, 95%CI: 1.19-10.24, $P = 0.023$). Furthermore, CPS antibiotic use (OR = 0.32, 95%CI: 0.10-0.97, $P = 0.044$) was significantly associated with improved CRP recovery rates within the same timeframe. It has been proposed that levels of vascular endothelial growth factor and nitric oxide are elevated during inflammatory states in animals, including cases of sepsis. CPS has been demonstrated to significantly reduce both parameters, which are strongly associated with the inflammatory response. Furthermore, the reduction in these biomarkers is linked to a decrease in CRP levels. This association may partially explain the mechanism by which CPS promotes a more rapid recovery in CRP levels[36]. These findings underscore the therapeutic advantage of CPS over CBP in this context.

The limitations of this study are that the retrospective case data were confined to a single-center analysis. Furthermore, children who experienced secondary complications after discharge may have been excluded from the statistical analysis, potentially leading to unreported data. Another limitation of this study was the classification of treatment groups based solely on the initial antibiotic regimen administered within the first 24 hours after admission. Postoperative modifications to antibiotic therapy might have influenced the outcomes. Nonetheless, given that such changes were infrequent, we adopted this classification approach, as we hypothesized that the ultimate antibiotic regimen would exert a more significant effect on postoperative PPA outcomes while minimizing potential sources of bias.

Future research directions include: (1) Investigating the mechanisms by which various antibiotics influence PPA prognosis, with a focus on basic research to uncover their molecular biological pathways; (2) Designing personalized perioperative antibiotic protocols to minimize adverse outcomes while maintaining effective control of inflammation; (3) Extending follow-up durations to evaluate the influence of perioperative factors on long-term complications associated with PPA; and (4) Undertaking multicenter, prospective studies to increase sample sizes and gather more comprehensive clinical data, particularly regarding perioperative antibiotic administration.

CONCLUSION

In summary, this retrospective analysis of clinical data from 65 patients with PPA identified the choice between CBP and CPS antibiotics as an independent determinant of CRP recovery rates within the first 7 days after surgery. Notably, CPS demonstrated comparable, if not superior, efficacy to CBP in managing PPA, achieving similarly favorable clinical outcomes.

FOOTNOTES

Author contributions: Hang T, Jiang XH and Zhu WC designed the research study; Jiang XH and Zhu WC review the research process and manuscript; Hang T, Chen QL, Li YH and Wang SW performed the research; Hang T, Chen QL writing-original draft preparation; Hang T and Chen QL writing-review and editing; Hang T and Chen QL data curation; Hang T, Chen QL, Li YH and Wang SW formal analysis. All authors have read and approve the final manuscript. Hang T and Chen QL contributed equally to this work as co-first authors. Both Jiang XH and Zhu WC have contributed equally to the roles expected of a corresponding author, as defined by your journal's guidelines. Specifically: (1) Academic leadership: Author Jiang XH led the fieldwork/data analysis/theoretical framework and oversaw the integration of interdisciplinary methodologies. Author Zhu WC directed the research design/clinical validation/technical development and coordinated collaborations with external partners; (2) Responsibility for communication: Author Jiang XH will handle inquiries related to methodology and data curation. Author Zhu WC will manage questions regarding clinical implications and technical details; and (3) Institutional requirements: This work was jointly supported by Jiaxing Maternity and Child Health Care Hospital and The First Affiliated Hospital of Ningbo University, and both institutions recognize the dual corresponding authorship to reflect the collaborative nature of the project.

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ORIGINAL ARTICLE

Retrospective Study

Role of pelvimetry in predicting surgical outcomes and morbidity in rectal cancer surgery: A retrospective analysis

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Abstract

BACKGROUND

Rectal cancer has increased in incidence, and surgery remains the cornerstone of multimodal treatment. Pelvic anatomy, particularly a narrow pelvis, poses challenges in rectal cancer surgery, potentially affecting oncological outcomes and postoperative complications.

AIM

To investigate the relationship between radiologically assessed pelvic anatomy and surgical outcomes as well as the impact on local recurrence following rectal cancer surgery.

METHODS

We retrospectively analyzed 107 patients with rectal adenocarcinoma treated with elective rectal surgery between January 1, 2017, and September 1, 2022. Pel-

vimetric measurements were performed using computed tomography (CT)-based two-dimensional methods (n = 77) by assessing the pelvic inlet area in mm², and magnetic resonance imaging (MRI)-based three-dimensional techniques (n = 52) using the pelvic cavity index (PCI). Patient demographic, clinical, radiological, surgical, and pathological characteristics were collected and analyzed in relation to their pelvimetric data.

RESULTS

When patients were categorized based on CT measurements into narrow and normal/wide pelvis groups, a significant association was observed with male sex, and a lower BMI was more common in the narrow pelvis group (P = 0.002 for both). A significant association was found between a narrow pelvic structure, indicated by low PCI, and increased surgical morbidity (P = 0.049). Advanced age (P = 0.003) and male sex (P = 0.020) were significantly correlated with higher surgical morbidity. Logistic regression analysis identified four parameters that were significantly correlated with local recurrence: older age, early perioperative readmission, longer operation time, and a lower number of dissected lymph nodes (P < 0.05). However, there were no significant differences between the narrow and normal/wide pelvis groups in terms of the operation time, estimated blood loss, or overall local recurrence rate (P > 0.05).

CONCLUSION

MRI-based pelvimetry may be valuable in predicting surgical difficulty and morbidity in rectal cancer surgery, as indicated by the PCI. The observed correlation between low PCI and increased surgical morbidity suggests the potential importance of a preoperative MRI-based pelvimetric evaluation. In contrast, CT-based pelvimetry did not show significant differences in predicting surgical outcomes or cancer recurrence, indicating that the utility of pelvimetry alone may be limited in these respects.

Key Words: Rectal cancer; Pelvimetry; Pelvic cavity index; Imaging techniques; Surgical outcomes; Morbidity; Local recurrence

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Core Tip: This study investigates the role of pelvimetry in predicting surgical and oncological outcomes in rectal cancer patients. Using computed tomography (CT)-based pelvic inlet area measurements and magnetic resonance imaging-based pelvic cavity index (PCI), the study identifies lower PCI as a significant predictor of surgical morbidity. However, CT-based pelvimetry showed no significant correlation with operation time or local recurrence. Multivariate analysis highlights age, sex, and PCI as independent risk factors for morbidity. While pelvimetry is useful for assessing surgical complexity, its value in predicting oncological outcomes remains limited, warranting further validation through larger multicenter studies.

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INTRODUCTION

The increasing incidence of rectal cancer highlights its importance as a major health concern, with surgery being the cornerstone of multimodal treatment[1,2]. Total mesorectal excision (TME) plays a critical role in rectal cancer surgery by significantly improving survival rates and reducing the risk of local recurrence[3]. However, ensuring optimal surgical and oncological outcomes can be challenging, particularly in patients with a narrow pelvis, as it is a recognized risk factor for increased postoperative complications. This is primarily because of the technical difficulties associated with performing TME in a limited pelvic cavity[4].

Though it is not widely adopted in routine clinical practice due to time constraints, pelvimetry provides valuable insights into bony pelvic anatomy and its relationship with surgical and oncological outcomes[5,6]. Pelvimetry can be performed using either magnetic resonance (MR) imaging (MRI) or computed tomography (CT) scans, which offer both 2D and 3D imaging capabilities. Although CT pelvimetry provides the convenience of simple assessment and quick and thorough scanning, MR pelvimetry provides a superior evaluation of adjacent structures and the mesorectum because of its heightened sensitivity to soft tissues[7].

The structure of the pelvic bone in two dimensions can be determined by measuring various parameters such as the interspinous distance, transverse inlet diameter, and midsagittal diameter[8]. These measures can be approximated in 3D using certain calculations and software[9]. There is growing interest in this field, as more studies have highlighted its potential benefits in surgical planning and risk assessment[10].

In this study, we employed two different imaging techniques by incorporating both CT-based- and MRI-based pelvimetric measurements. The CT-based method provides 2D analysis of the pelvic inlet area[11], allowing for a basic and effective assessment of the pelvic structure. MRI-based pelvimetric assessments, specifically the pelvic cavity index (PCI), were used to provide a detailed 3D evaluation of the pelvic structure. PCI was chosen because of its ability to integrate multiple anatomical measurements, offering a more comprehensive understanding of pelvic anatomy. This method has been validated in previous studies for its relevance in assessing surgical complexity, particularly in confined pelvic spaces, and for its predictive value for surgical and oncological outcomes[12]. By employing PCI, we aimed to enhance the precision of pelvic assessment and address the limitations of two-dimensional measurements.

By integrating both imaging modalities, our study sought to address gaps in the literature, as most reports relied on either CT or MRI alone. We aimed to provide a more robust understanding of how pelvic anatomy influences surgical difficulty, postoperative morbidity, and oncological outcomes of rectal cancer surgery. Ultimately, our findings could inform clinical practice, help optimize surgical planning, and improve patient outcomes.

The primary objective of our study was to investigate the relationship between radiologically assessed pelvic anatomy and surgical outcomes (perioperative morbidity and mortality, operation time, estimated blood loss, length of hospital stay, pelvic infection, local recurrence, anastomotic leak, readmission, estimated blood loss) in patients with rectal cancer. The secondary objective was to evaluate the relationship between the pelvic structure and local recurrence following rectal cancer surgery.

We hypothesized that rectal cancer patients with a narrow pelvic structure, as assessed by pelvimetric analysis, would have poorer surgical outcomes and lower oncological surgical quality. The oncological surgical quality in our study was evaluated based on the total number of dissected lymph nodes reported in routine pathology reports.

MATERIALS AND METHODS

Study design and patient selection

Our study retrospectively analyzed cases of rectal surgery (low anterior resection, abdominoperineal resection) performed electively as open or laparoscopic procedures in patients diagnosed with "rectal adenocarcinoma" at the General Surgery Clinic of SBÜ Bursa Yüksek İhtisas Training and Research Hospital between January 01, 2017 and September 01, 2022. A total of 107 patients were included in this study. The patients included in the study were over 18 years of age and had clinical, pathological, and surgical data accessible through the hospital's data system and archives. For radiological parameters, patients with available CT or pelvic MRI data were included.

The exclusion criteria were designed to eliminate pathologies that could interfere with the establishment of a direct relationship between pelvic structure and surgical or oncological outcomes. This approach was adopted to ensure the homogeneity of the study population and was consistent with the methodologies described in the literature. The exclusion criteria included patients who underwent emergency Hartmann's procedure (n = 11), patients who underwent surgery for synchronous tumors (n = 3), patients who did not complete neoadjuvant therapy (n = 3), patients with adjacent organ invasion (T4b tumor, n = 5), patients with distant metastasis (n = 2), patients who underwent surgery for familial adenomatous polyposis (n = 1), and patients without accessible radiological data (n = 3; Figure 1). Preoperative, operative, and postoperative data were obtained from the hospital data system and the patient files.

Treatment planning

All patients diagnosed with rectal adenocarcinoma in our clinic were evaluated for treatment planning by a multidisciplinary tumor board consisting of the Departments of General Surgery, Oncology, Radiology, Pathology, and Nuclear Medicine. Patients were evaluated using complete colonoscopy, routine blood tests (including complete blood count, biochemistry, and tumor markers such as CEA, CA 19-9, CA 15-3, and radiological examinations (thoracic and abdominal CT and pelvic MRI). In our study, the rectal tumor localization was classified as upper (10-15 cm), middle (5-10 cm), or lower (0-5 cm). Patients were staged and treated according to the National Comprehensive Cancer Network colorectal cancer TNM guidelines. Neoadjuvant chemoradiotherapy, managed by the oncology and radiation oncology departments, consisted of two weeks of radiotherapy and two cycles of 5-fluorouracil infusion. The proposed treatment plan was implemented with patient consent; however, the tumor board did not convene for 9 mo due to quarantine measures during the pandemic, and patient management during this period was determined through consultations.

Surgical planning was based on the individual experience of the primary surgeon, tumor localization, preoperative evaluation, and preference for laparoscopic or open procedures. The rectal cancer surgeries evaluated in this study included open low anterior resection, laparoscopic low anterior resection, and abdominoperineal resection. TME was performed in all surgical cases using a standardized laparoscopic technique for each surgeon using the double-stapling technique (dividing the rectum with a linear stapler and creating anastomosis with a circular stapler).

Data collection

Patient demographics and characteristic parameters [age, sex, American Society of Anesthesiologists Score (ASA), body mass index (BMI)], neoadjuvant status, operative data [open/laparoscopic low anterior resection, miles operation, ileostomy status, tumor localization (upper, middle, lower)], pathological results (tumor size, mesorectum status, T-N stage, pathological stage, lymph node count, lymphovascular invasion), surgical outcomes (operative time, estimated blood loss, hospital stay, pelvic infection, local recurrence, anastomotic leak, readmission, morbidity, and mortality), radiological pelvic assessment data (pelvic inlet area measured by CT and PCI by MRI), and postoperative follow-up data (follow-up duration, adjuvant therapy, disease-free survival, overall survival, and recurrence) were collected.

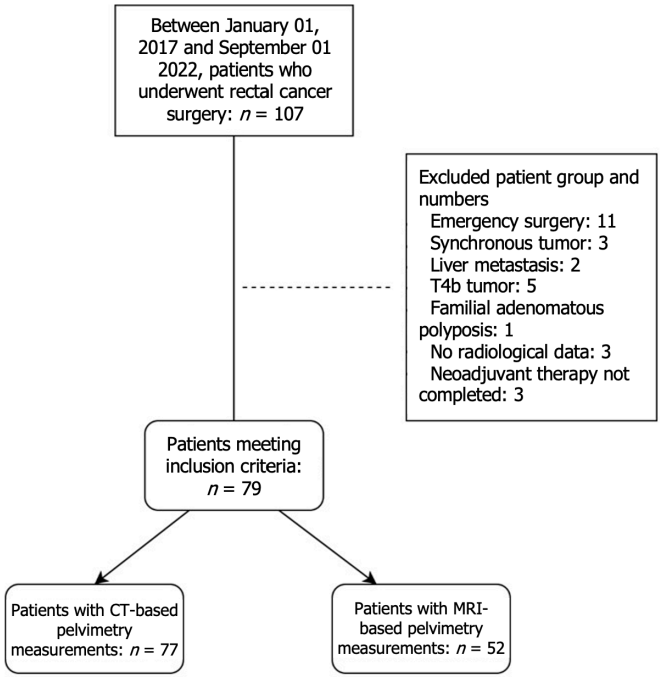


Figure 1 Flowchart of research methodology. CT: Computed tomography.

Surgical difficulty was assessed by evaluating operation time, estimated blood loss, length of hospital stay, and perioperative morbidity. The assessment of specimen quality was determined by lymph node count, as the status of the mesorectum was not consistently included in the pathology reports. Due to the low mortality rate, it was not possible to perform statistical analysis on overall survival and disease-free survival. Oncological outcomes were assessed based on local recurrence.

Pelvic infection was defined as the presence of a collection in the pelvic region and elevated inflammatory parameters without anastomotic leakage. Local recurrence was defined as any recurrent tumor growth in the pelvic or perineal region as confirmed by clinical, radiological, or pathological assessments without time restriction. Pathological variables were obtained from routine pathology reports; however, mesolectal status" was not consistently reported during the study period and was thus not included as a variable in the statistical analysis.

Operative morbidity, as defined in the literature, refers to temporary or permanent disorders that occur between the day of surgery and beginning of data collection. In our study, the postoperative morbidity within 30 days was used as a variable. Surgical mortality, as defined in the literature, refers to deaths occurring within the first 30 days postoperatively regardless of the cause (in-hospital or out-of-hospital). Early recurrence was defined as recurrence at the surgical site or distant organ metastasis within the first year after the surgery.

Pelvimetric measurements

Two different methods were used for pelvimetric analysis in the included patients: CT-based- and MRI-based. The definition of "narrow pelvis" was based on the following threshold values for the CT-based method and quantitative analysis for the MRI-based method.

CT-based pelvimetry: Radiological assessment of the pelvic structure using CT (CT pelvimetry) was performed using a multidetector CT scanner (Revolution Maxima, GE Health Care, United States), and CT datasets were analyzed using the Sekans Ankara Picture Archiving and Communication System (Figure 2). Pelvic inlet area measurement and classification of pelvic structure as narrow or wide were conducted using the automatic measurement method described by Noh *et al* [6], with the threshold value (8800 mm²) they determined. To determine the area, the anteroposterior (AP) pelvic diameter (distance from the posterior border of the symphysis pubis to the tip of the coccyx) and the transverse pelvic diameter (distance between the inner borders of the lateral bony pelvis perpendicular to the AP diameter) were considered. Patients with a pelvic area < 8800 mm² were classified as having a narrow pelvis, whereas those with an area ≥ 8800 mm² were classified as having a normal/wide pelvis (Figure 2). CT Pelvimetry reflects the characteristics of the pelvic structure based on a 2D approach.

MRI-based pelvimetry and PCI: Pelvic MRI examinations were performed using Philips Gyroscan NT15 Intera 1.5. MRI-based pelvimetric measurements were performed in sagittal and axial sections of the T2 phase with the support of a radiology clinic. The PCI, which reflects the 3D character of the pelvic structure, was calculated using the formula (pelvic inlet × interspinous distance/pelvic depth; Figure 3)[9]. PCI was first described by Hong *et al*[13] in 2009 to assess the impact of the pelvic structure on robot-assisted laparoscopic prostatectomy. According to this calculation, a wider and shallower pelvic structure will have a higher PCI (cm) value, whereas a narrow and deep pelvis will have a lower PCI value.

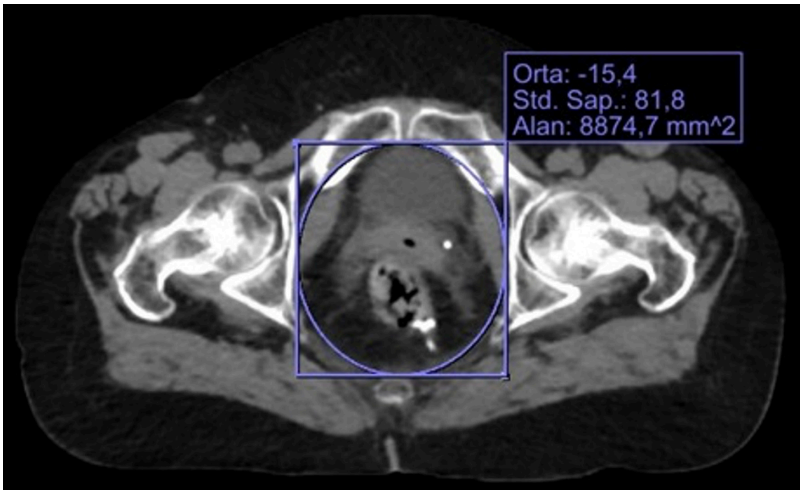


Figure 2 Pelvic inlet area is calculated using the Picture Archiving and Communication System.

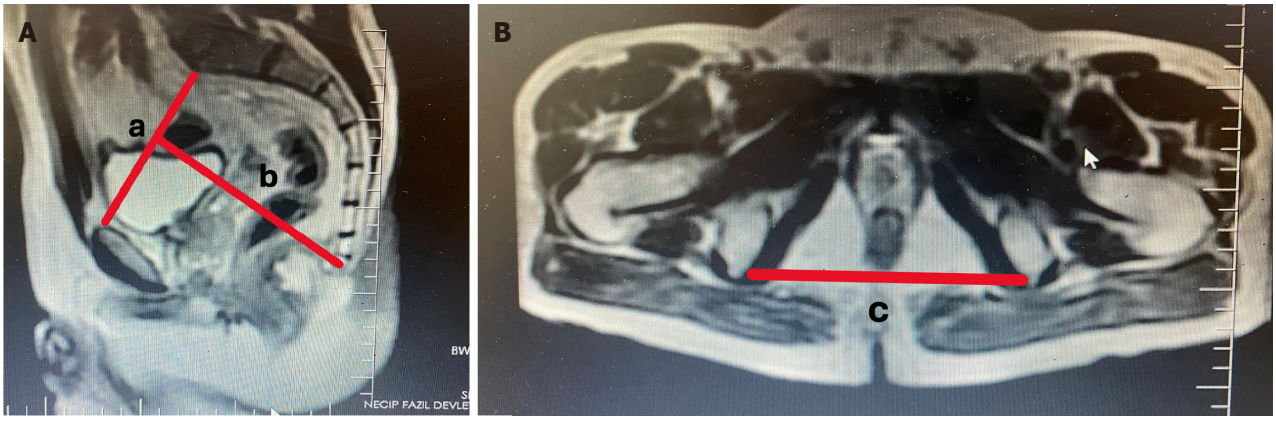


Figure 3 Magnetic resonance imaging-based calculation of the pelvic cavity index. A: Measurement of pelvic inlet diameter and pelvic depth in sagittal section using magnetic resonance imaging; B: Measurement of interspinous distance using magnetic resonance imaging [pelvic cavity index: (a.c/b)].

Statistical analysis

Methods for data analysis: The Shapiro-Wilk test was used to determine whether continuous variables followed a normal distribution. Mean and standard deviation values were provided for variables with a normal distribution, whereas median, minimum, and maximum values were provided for variables that did not follow a normal distribution. Based on the results of the normality test, comparisons between two groups were made using the Mann-Whitney *U* test and independent *t*-test. If the number of groups exceeded two, the Kruskal-Wallis test was used. If overall significance was found after the Kruskal-Wallis test, post- hoc subgroup analyses were conducted using the Dunn-Bonferroni test. Categorical variables were compared between the groups using Pearson's χ^2 test, Fisher's exact χ^2 test, and Fisher-Freeman-Halton test. The relationship between continuous variables was determined by correlation analysis, and Pearson and Spearman correlation coefficients were calculated. The factors affecting local recurrence and surgical morbidity were investigated using logistic regression analysis. Receiver operating characteristic analysis was performed to evaluate the effectiveness of BT mm² measurement in identifying the groups associated with recurrence and surgical outcomes. Statistical analyses were performed using the SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.) and MedCalc (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2022) software, and a P value < 0.05 was considered statistically significant.

Bias minimization strategies: Efforts were made to minimize potential sources of bias in this study. Strict inclusion and exclusion criteria were applied to ensure a homogeneous study population, which included only patients with complete clinical, radiological, and pathological data. Retrospective data collection was performed using reliable sources, such as electronic medical records, imaging studies, and surgical notes, to ensure accuracy and consistency. Additionally, to reduce observer bias, all pelvic measurements were conducted by experienced radiologists who were blinded to the clinical outcomes. Statistical adjustments were made using multivariate analyses to control for confounding variables such as age, sex, and BMI. These measures collectively aimed to enhance the validity and reliability of the study's findings.

Management of incomplete data: For each parameter with missing values, cases specific to that parameter were excluded from the analysis. This approach ensures that only complete and reliable data contributed to the evaluation of each variable. Patients with missing key parameter values were excluded from the study to maintain consistency and validity of the analysis. This method minimized the impact of incomplete data on the study outcomes and preserved the robustness of the findings. The proportion of cases excluded due to missing data was reported to ensure transparency.

Rationale for sensitivity analysis exclusion: No formal sensitivity analysis was conducted in this study. However, the robustness of the findings was supported by strict adherence to the inclusion and exclusion criteria, which ensured a homogeneous study population. For parameters with missing data, a complete case analysis approach was employed to minimize bias and maintain the validity of the results. Given the limited sample size, sensitivity analyses were deemed unnecessary because the dataset was comprehensive for the selected variables and outcomes. Further studies with larger cohorts are needed to explore the potential impact of alternative analytical methods.

RESULTS

Demographic and baseline characteristics

Table 1 summarizes the demographic, clinical, radiological, surgical, and pathological characteristics of patients included in the study. The average number of dissected lymph nodes in the surgeries was found to be 14.75, and the PCI value was 10.40. It was observed that 48.10% of the patients received neoadjuvant therapy, and 67.60% of the patients were directed to adjuvant therapy. The mean follow-up duration was 32 mo (Table 1).

Data on BMI for six patients, ASA score for one patient, and surgical parameters for one patient were unavailable. Because fecal diversion was excluded except for patients who underwent Miles operations, the sample size was 73. Pelvimetric analysis was performed on 77 patients with CT images from 52 patients and MRI images from 79 patients. Due to the absence of data in the pathology report, tumor stage in one patient, tumor size in two patients, lymph node count in two patients, and lymphovascular status in five patients could not be assessed.

Pelvimetric analysis findings and surgical outcomes

Table 2 shows the comparison of demographic, pathological, and clinical variables among the patient groups based on CT measurements. Male sex and BMI were significantly associated with a narrow pelvis (both $P = 0.002$). The proportion of male patients was higher in the narrow pelvis group, and their mean BMI (25.42 kg/m^2) was lower than that in the normal pelvis group (28.93 kg/m^2). No significant differences were observed in other variables ($P > 0.05$). The mean PCI value, reflecting the three-dimensional structure of the pelvis, was lower in the group classified as having a narrow pelvis based on two-dimensional CT, with an average of 10.13 compared to 10.8, but this difference was not statistically significant (Table 2). For this table, data on BMI for six patients, operation time for one patient, pathological tumor stage for one patient, tumor size for two patients, and lymph node count for one patient were unavailable. There was a total of 52 patients with MRI images.

Table 3 focuses on the surgical outcomes of the patient groups based on CT measurements. In the comparison based on CT-assisted pelvimetry, no significant differences were found in the surgical outcomes between the study groups ($P > 0.05$). For this table, data on the operation time for one patient, estimated blood loss for one patient, and lymph node count for two patients were unavailable. Because we had two cases of perioperative surgical mortality, the recurrence parameter was evaluated with $n = 75$. Additionally, as two of our patients were lost due to coronavirus disease 2019 (COVID-19) infection (not considering surgical mortality within 30 days postoperatively), the readmission parameter was evaluated based on 72 patients. For the anastomotic leak variable, after excluding patients who underwent Miles operation, the number of patients for whom CT-assisted pelvimetry analysis could be performed was 70 (Table 3).

Table 4 addresses the comparison of patient groups with and without perioperative morbidity. Significant differences were observed in terms of age ($P = 0.003$), sex distribution ($P = 0.020$), and the PCI ($P = 0.049$). Patients in the morbidity group had a higher average age (71.70 years) than those without morbidity (63.52 years). The proportion of male patients was significantly higher in the morbidity group (85.19%) than in the nonmorbidity group (59.62%). Additionally, the mean PCI value was lower in the morbidity group (9.62) than in the non-morbidity group (10.78). No significant differences were found between the groups for any other variables ($P > 0.05$; Table 4).

Subgroup analysis according to operation type

In the subgroup analysis (Table 5), the operative time was significantly longer in the open low-anterior group than in the laparoscopic low-anterior group ($P = 0.040$). Similarly, the length of hospital stay was significantly longer in the open low anterior group than in the laparoscopic low anterior group ($P < 0.001$). No statistically significant differences were found among the groups in any of the other parameters ($P > 0.05$).

Oncological outcomes and pelvimetric analysis findings

No significant differences were found between the groups with or without recurrence based on patients' demographic, pathological, and pelvimetric characteristics ($P > 0.05$; Table 6).

Multivariate analysis and predictive performance

To identify risk factors for surgical morbidity, variables were first analyzed using univariate logistic regression, and those

Table 1 Distribution of demographic, surgical, pathological, clinical, and radiological characteristics of the patients included in the study

Items	Value
Age (years; *n* = 79)	66.32 ± 11.87
Gender (*n* = 79)	
Male	54 (68.35)
Female	25 (31.65)
BMI (kg/m^2; *n* = 73)	25.90 (19:44)
Tumor localization (*n* = 79)	
Upper rectum	30 (37.97)
Middle rectum	16 (20.25)
Lower rectum	33 (41.77)
ASA score (*n* = 78)	
I	1 (1.28)
II	30 (38.46)
III	46 (58.97)
IV	1 (1.28)
Operation type (*n* = 79)	
Open low anterior	36 (45.57)
Laparoscopic low anterior	37 (46.84)
Miles	6 (7.59)
Operation time (min; *n* = 78)	237.12 ± 59.82
Blood loss cc (*n* = 78)	125 (50:200)
Tumor stage (n = 78)	
0	5 (6.41)
1	21 (26.92)
2A	17 (21.79)
2B	3 (3.85)
3A	14 (17.95)
3B	9 (11.54)
3C	9 (11.54)
Tumor size (cm; *n* = 77)	3.50 (0:17)
Pelvic inlet area-CT mm^2 (*n* = 77)	8428.65 ± 1232.66
Fecal diversion (*n* = 73)	
Exist	48 (65.75)
None	20 (27.40)
Lymphovascular invasion (*n* = 74)	23 (29.90)
Average number of lymph nodes dissected (*n* = 77)	14.75 ± 7.99
PCI (*n* = 52)	10.40 ± 2
Neoadjuvant therapy (*n* = 79)	38 (48.10)
Adjuvant therapy (*n* = 74)	50 (67.60)
Follow-up period (months; *n* = 75)	32 (0:70)

Data are expressed as *n* (%), mean ± SD, and median (minimum:maximum). ASA: American Society of Anesthesiologists; CT: Computed tomography; BMI: Body mass index; PCI: Pelvic cavity index.

Table 2 Comparisons based on demographic, pathological, and clinical variables among patient groups formed according to computed tomography measurements

	n	Narrow	*n*	Normal	*P* value
Age (years)	48	67.13 ± 11.84	29	64.86 ± 11.96	0.421[a]
Gender (*n* = 79)					
Male	48	39 (81.25)	29	14 (48.28)	0.002[b]
Female		9 (18.75)		15 (51.72)	
BMI (kg/m^2)	46	25.42 ± 3.96	2	28.93 ± 5.15	0.002[a]
Tumor localization					
Upper rectum	48	20 (41.67)	29	10 (34.48)	0.532[b]
Middle rectum		11 (22.92)		5 (17.24)	
Lower rectum		17 (35.42)		14 (48.27)	
ASA score					
I	48	1 (2.08)	28	0	0.318[c]
II		15 (31.25)		14 (50)	
III		31 (64.58)		14 (50)	
IV		1 (2.08)		0	
Operation type					
Open low anterior	48	24 (50)	29	11 (37.93)	0.281[c]
Laparoscopic low anterior		22 (45.83)		14 (48.28)	
Miles		2 (4.17)		4 (13.79)	
Tumor stage					
0	47	1 (2.13)	29	4 (13.79)	0.604[c]
1		13 (27.66)		8 (27.59)	
2A		11 (23.40)		6 (20.69)	
2B		2 (4.26)		1 (3.45)	
3A		7 (14.89)		5 (17.24)	
3B		6 (12.77)		3 (10.34)	
3C		7 (14.89)		2 (6.90)	
Tumor size (cm)	46	4 (0:17)	29	3 (0:7)	0.052[d]
PCI	31	10.13 ± 1.99	21	10.80 ± 2	0.236[a]

[a]Independent samples *t*-test.
[b]χ^2 test.
[c]Fisher-Freeman-Halton test.
[d]Mann-Whitney *U* test.
Data are expressed as *n* (%), mean ± SD, and median (minimum:maximum). ASA: American Society of Anesthesiologists; BMI: Body mass index; PCI: Pelvic cavity index.

with $P < 0.25$ were included in a multivariate logistic regression model (Table 7). The final model identified age, sex, and PCI as significant factors that influence morbidity. The model demonstrated a good fit with the data (Hosmer-Lemeshow test, $P = 0.167$) and was statistically significant ($P < 0.001$).

The variables were initially examined using univariate logistic regression to determine risk factors contributing to local recurrence. Only variables with $P < 0.25$ were included in the multivariate logistic regression model. Variables that met

Table 3 Comparison of surgical outcomes among patient groups formed according to computed tomography measurements

	n	Narrow	*n*	Normal	*P* value
Operation time (min)	47	237.66 ± 57.43	29	233.97 ± 65.33	0.797[a]
Blood loss (cc)	48	137.50 (50:200)	28	125 (50:200)	0.723[d]
Length of stay (day)	48	8 (4:32)	29	7 (4:21)	0.462[d]
Readmission					
Exist	44	8 (53.33)	28	7 (46.67)	0.487[b]
None		36 (63.16)		21 (36.84)	
Dissected lymph nodes	46	15 (1:42)	29	13 (2:30)	0.229[d]
Pelvic infection					
Exist	48	6 (60)	29	4 (40)	> 0.99[c]
None		42 (62.69)		25 (37.31)	
Recurrence	45	9 (20)	30	6 (20)	0.943[b]
Anastomosis leakage	44	5 (62.50)	26	3 (37.50)	> 0.99[c]
Perioperative morbidity	48	19 (70.37)	29	8 (29.63)	0.285[b]
Surgical mortality	48	1 (50)	29	1 (50)	0.645[c]

[a]Independent sample *t* test.
[b]χ^2 test.
[c]Fisher's exact χ^2 test.
[d]Mann Whitney *U* test.
Data are expressed as *n* (%), mean ± SD, and median (minimum:maximum).

the requirements and were included in the multivariate model were age, surgery time, total number of lymph nodes, and occurrence of readmission. A forward selection method was used for variable selection. The findings are displayed in Table 8 and demonstrate that the model is an appropriate fit for the data based on the Hosmer-Lemeshow test (P = 0.694) and is statistically significant (P = 0.009). Each additional unit of operation time was linked to a 1% reduction in the likelihood of experiencing local recurrence. In addition, individuals who experienced readmission had a risk of recurrence that was 6.07 times higher than patients who never underwent readmission (Table 8).

DISCUSSION

This study explored the associations of MRI-based PCI measurements (3D) and CT-based pelvic inlet area assessments (2D) with surgical outcomes, perioperative morbidity, and local recurrence. Although a narrow pelvis was associated with longer operative times and increased estimated blood loss, these differences were not statistically significant. Additionally, low PCI values demonstrated a significant correlation with increased perioperative morbidity (P = 0.049); however, no notable differences in other surgical and oncological outcomes were observed between the narrow and normal/wide pelvis groups.

In statistical analyses, we evaluated the morbidity parameter as a categorical variable, and we did not utilize the numerical Clavien-Dindo classification. The morbidities observed included atelectasis, pneumonia, urinary retention, postoperative ileus, wound infection, anastomotic leakage, and pelvic collection. Two patient deaths were caused by sepsis and multi-organ failure that occurred following anastomotic leakage, while the other death was a result of delayed bleeding from the epigastric artery during the laparoscopic procedure. Statistical analysis of surgical morbidity cases revealed a strong association between advanced age (P = 0.003) and male sex (P = 0.020).

Several studies have specifically investigated the correlation between morbidity and pelvimetry in rectal cancer surgery, with an emphasis on anastomotic leakage. Tsuruta *et al*[14] found that using MRI to identify a narrow pelvis with a PCI value of 13 was useful for predicting anastomotic leaks. According to Atasoy *et al*[9], pelvic depth is linked to anastomotic leaks on MRI. Conversely, the research conducted by Zur Hausen *et al*[15] failed to find any correlation between pelvimetric readings and anastomotic leakage. Consistent with Zur Hausen *et al*[15], our study did not identify a statistically significant relationship between pelvimetric parameters and anastomotic leakage (P > 0.05).

Several studies have examined the correlation between operative time and pelvimetry, which can be considered as an indicator of surgical complexity in rectal cancer surgery. Yan *et al*[16] conducted CT-based pelvimetric analysis and found that the interspinous distance, length of the pelvic inlet, and distance from the sacral promontory to the coccyx tip were associated with longer operating times. Zhou *et al*[17] found that the AP diameter of the pelvic inlet, AP diameter of the pelvic outlet, height of the pubic symphysis, sacrococcygeal distance, sacrococcygeal-pubic angle, and diameter of the

Table 4 Comparisons between patient groups with or without perioperative morbidity

	n	Exist	*n*	None	*P* value
Age (year)	27	71.70 ± 9.16	52	63.52 ± 12.22	0.003[a]
Gender					
Male	27	23 (85.19)	52	31 (59.62)	0.020[b]
Female		4 (14.81)		21 (40.38)	
BMI (kg/m^2)	23	27.60 (19:44)	50	24.90 (19.50:37.70)	0.316[d]
Tumor localization					
Upper rectum	27	12 (44.44)	52	18 (34.62)	0.588[b]
Middle rectum		4 (14.81)		12 (23.08)	
Lower rectum		11 (40.74)		22 (42.31)	
ASA score					
I	27	0	51	1 (1.96)	0.583[c]
II		11 (40.74)		19 (37.25)	
III		15 (55.56)		31 (60.78)	
IV		1 (3.70)		0	
Operation time (min)	27	240 (130:360)	51	240 (150:360)	0.782[d]
Blood loss (cc)	26	137.50 (50:200)	52	125 (50:200)	0.355[d]
Tumor size	25	3.50 (0.03:17)	52	3.75 (0:8.40)	0.836[d]
Pelvic inlet area-CT (mm^2)	27	8449.29 ± 1043.45	50	8417.50 ± 1333.64	0.915[a]
Number of dissected lymph nodes	25	13 (3:32)	52	15 (1:42)	0.372[d]
PCI	17	9.62 ± 1.74	35	10.78 ± 2.03	0.049[a]

[a]Independent samples *t*-test.
[b]χ^2 test.
[c]Fisher-Freeman-Halton test.
[d]Mann-Whitney *U* test.
Data are expressed as *n* (%), mean ± SD, and median (minimum:maximum). ASA: American Society of Anesthesiologists; CT: Computed tomography; BMI: Body mass index; PCI: Pelvic cavity index.

upper pubis to the coccyx affect the duration of surgery when using CT pelvimetry. A study by Noh *et al*[6] found that a narrow pelvis did not have an impact on the duration of the surgical procedure, as determined by CT scans. Consistent with Noh *et al*[6], we did not identify any correlation between pelvimetric parameters and operative time or estimated blood loss ($P > 0.05$).

In the literature, the relationship between surgical quality and pelvimetry in rectal cancers has been analyzed using specimen evaluation and circumferential resection margin (CRM) status[7]. According to the literature, a short interspinous distance has a negative effect on the TME quality[2,15]. The usefulness of pelvimetry in predicting involvement of CRM is debated in the literature. Yamaoka *et al*[18] were unable to establish a statistical relationship, but Chau *et al*[19] found statistical significance. In our study, surgical quality was evaluated using the lymph node count reported in pathology assessments. CT-based pelvimetry revealed no significant differences in lymph node counts between patients with narrow and normal pelvises ($P > 0.05$).

Upon comparing the demographic and patient characteristic data of the cases in our study with existing studies on pelvimetry in rectal cancer surgery, we believe that our study included a relatively higher proportion of elderly patients with comorbidities. The patient profile in this study was predominantly male, which aligns with the previous findings. Additionally, the average BMI in this study was higher than that in Eastern studies[6,9,15,20,21]. This highlights the importance of considering patient characteristics in the context of pelvimetry-related outcomes and their generalizability to broader populations.

When comparing our surgical outcomes with the literature, we observed that our average operative time was longer (237.12 min), and our estimated blood loss was higher (125 cc). We attributed these differences to the quality of documentation and the fact that the surgeries were performed by 11 surgeons in a general surgery clinic. Other statistics included the average number of removed lymph nodes (14.75), laparoscopic surgery rate (46%), conversion to open surgery rate (13%), surgical morbidity rate (34%), mortality rate (2.5%), average hospital stay (7.4 d), and anastomotic leakage rate (11%). We consider the shorter average hospital stay in comparison with the existing literature to be a positive aspect. Additionally, our morbidity rate and surgical outcomes are partially aligned with those reported in the

Table 5 Comparison of surgical outcomes according to operation type

	n	Open low anterior	*n*	Laparoscopic low anterior	*n*	Miles	*P* value
Operation time (min)	36	240 (165:360)	36	210 (130:360)	6	270 (180:360)	0.023[c]
Length of hospital stay (days)	36	9.50 (5:32)	37	7 (4:32)	6	9 (6:19)	< 0.001[c]
Readmission							
Present	33	7 (21.21)	35	6 (17.14)	6	2 (33.33)	0.684[b]
Absent		26 (78.79)		29 (82.86)		4 (66.67)	
Dissected lymph nodes	34	15 (1:29)	34	12 (2:42)	6	20 (2:30)	0.389[c]
Pelvic infection							
Present	36	7 (19.44)	37	3 (8.11)	6	0	0.308[b]
Absent		29 (80.56)		34 (91.89)		6 (100)	
Local recurrence	34	6 (17.60)	35	9 (25.70)	6	0	0.378[a]
Anastomotic leakage	33	5 (15.15)	36	3 (8.33)	0	0	0.527[a]
Surgical morbidity	36	15 (41.67)	37	11 (29.73)	1	1 (16.67)	
Surgical mortality	36	3 (8.33)	37	2 (5.41)	6	0	0.783[a]

[a]Fisher-Freeman-Halton test.
[b]Fisher's exact χ^2 test.
[c]Kruskal-Wallis test.
Data are expressed as *n* (%) and median (minimum:maximum).

literature[6,20,21].

Various techniques have been used to assess the relationship between pelvic anatomy and rectal cancer surgery. Analysis of CT-based research in the literature showed that Noh *et al*[6] observed a higher incidence of pelvic surgical site infection and local recurrence in patients with a narrow pelvic inlet area. However, they did not establish a correlation between surgical outcomes and pelvimetry. According to Bolshinsky *et al*[11], patients with a wide pelvic inlet showed a statistically significant improvement in quality. The research conducted by Gojayev *et al*[22] did not yield any statistically significant results in their study on the association between pelvic linear diameters and CRM involvement. Narrow pelvis categorization was correlated with male sex in three studies. Yasar *et al*[10] did not find any statistically significant relationship between pelvimetric measurements using 8 pelvic lengths, 2 angles, and operation time. Analysis of our data showed a statistically significant association between male sex and BMI with CT-based narrow pelvis classification (P = 0.002). At this point, it is important to remember that research in the literature indicates that the male sex is a risk factor for anastomotic leakage, thereby contributing to surgical morbidity[23,24].

Evaluation of MRI-based pelvimetric studies has revealed that a narrow pelvic inlet is linked to CRM involvement[25], incomplete TME[26], and intraoperative blood loss[9,27]. Multiple studies have demonstrated that shortened interspinous and intertubercular distances correlate with poor surgical outcomes. de'Angelis *et al*[28] showed that a small intertuberous distance increases the probability of conversion from laparoscopic to open surgery. Escal *et al*[29] found that a small intertuberous distance was linked to a higher surgical complexity in their scoring system.

A comparison between CT and MR pelvimetry revealed that while there is agreement in the literature on several length measurements, MR pelvimetry is more accurate for measuring the posterior sagittal diameter of the pelvic inlet and AP pelvic outlet diameter[30]. At this juncture, we believe that it is crucial to assess various methodologies and verify diverse approaches. Therefore, our objective was to enhance surgical prediction by incorporating parameters from different techniques. Based on our dataset, we observed a correlation between the reduced pelvic inlet area determined by CT and low PCI values determined by MR; however, this correlation was not statistically significant.

Based on our study, these data suggest that preoperative pelvic measurements are not significantly correlated with local recurrence. However, we found a correlation between local recurrence and readmission, longer operative time, age, and fewer lymph node dissections (P = 0.009). The local recurrence rate in our study was 18%, whereas a case series by Tersteeg *et al*[31] reported a rate of 4.4%. This study aimed to evaluate the effects of neoadjuvant therapy on local recurrence. The results showed that the clinical stage and lymph node count were significantly correlated with local recurrence. The study by Giesen *et al*[32] involved 1548 patients. They reported a local recurrence rate of 5% after a follow-up period of 36 months. This study compared local recurrence and survival rates based on the lymph node stage. In rectal cancer, the N stage has a substantial impact on local recurrence but no influence on survival. Based on two extensive case series in the literature, it is evident that the current local recurrence rate is higher for rectal cancers. This highlights the need to improve the effectiveness of multimodal treatment for rectal cancer and enhance the quality of surgical procedures.

Table 6 Demographic, pathological, clinical, and radiological comparisons based on local recurrence development

	n	Exist	*n*	None	*P* value
Age	15	70.13 ± 10.02	60	64.90 ± 12.29	0.132[a]
Gender					
Male	15	9 (60)	60	41 (68.33)	0.540[b]
Female		6 (40)		19 (31.67)	
BMI (kg/m^2)	14	25.40 (19:37.70)	56	25.60 (19.50:44)	0.959[d]
Tumor localization					
Upper rectum	15	5 (33.33)	60	23 (38.33)	0.768[b]
Middle rectum		4 (26.67)		11 (18.33)	
Lower rectum		6 (40)		26 (43.33)	
ASA score					
I	15	0	59	1 (1.69)	0.339[c]
II		6 (40)		22 (37.29)	
III		8 (53.33)		36 (61.02)	
IV		1 (6.67)		0	
Tumor stage					
0	15	2 (13.33)	59	3 (5.08)	0.720[c]
1		4 (26.67)		16 (27.12)	
2A		3 (20)		13 (22.03)	
2B		0		3 (5.08)	
3A		2 (13.33)		11 (18.64)	
3B		3 (20)		5 (8.47)	
3C		1 (6.67)		8 (13.56)	
Tumor size (cm)	15	3 (0.04:8.40)	58	4 (0:17)	0.612[d]
Pelvic inlet area-CT (mm^2)	15	8476.85 ± 1134.93	59	8431.43 ± 1292.23	0.901[a]
Number of dissected lymph nodes (*n*)	15	12.33 ± 4.97	58	15.10 ± 8.67	0.240[a]
PCI	11	10.50 ± 2.54	40	10.41 ± 1.87	0.915[a]

[a]Independent samples *t*-test.
[b]χ^2 test.
[c]Fisher-Freeman-Halton test.
[d]Mann-Whitney *U* test.
Data are expressed as *n* (%), mean ± SD, and median (minimum:maximum). ASA: American Society of Anesthesiologists; CT: Computed tomography; BMI: Body mass index; PCI: Pelvic cavity index.

This study has limitations. In nature, a dataset may contain both losses and biases. The small sample size of the patients might have failed to meet the criteria for scientific validation and generalization. A potential source of heterogeneity may have arisen from the inclusion of patients with upper, middle, and lower rectal cancers in the patient group. The evaluation of pre- and post-treatment responses in patients undergoing neoadjuvant therapy should be effective. Additionally, the absence of standardized reporting for TME quality restricts the comprehensive evaluation of surgical quality, which is crucial for understanding oncological outcomes. The variability in surgical outcomes may also have been influenced by the wide range of surgeons involved, highlighting the operator-dependent nature of rectal cancer surgery. The time interval hindered the collection of data on 5-year local recurrence, overall survival, and disease-free survival. The use of pre-established cut-off values for pelvimetric measurements from external studies may not fully reflect population-specific anatomical variations, further challenging the generalizability of the results. Finally, disruptions caused by the COVID-19 pandemic, including interruptions in multidisciplinary tumor board meetings, may have affected treatment planning and outcomes for a subset of patients. Given the limited scope of this study to a single institution, it is imperative to corroborate the results of additional research. Further investigation is necessary within a broader scope with scrupulous planning.

Table 7 Risk factors affecting perioperative surgical morbidity, regression analysis

	Univariate logistic regression model		Multivariate logistic regression model	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (years)	1.07 (1.02-1.12)	0.005		
Gender (male)	3.90 (1.18-12.90)	0.026		
BMI	1.05 (0.94-1.16)	0.402		
Tumor localization (upper rectum)		0.592		
Middle rectum	0.50 (0.13-1.92)	0.313		
Lower rectum	0.75 (0.27-2.10)	0.583		
ASA score	1.15 (0.48-2.76)	0.747		
Operation type (open low anterior)		0.375		
Laparoscopic low anterior	0.59 (0.23-1.56)	0.289		
Miles	0.28 (0.03-2.65)	0.267		
Operation duration	1 (0.99-1.01)	0.637		
Blood loss (cc)	1 (0.99-1.02)	0.325		
Tumor stage (0)		0.993		
1	1.33 (0.14-12.82)	0.803		
2A	1.23 (0.24-6.36)	0.804		
2B	1.09 (0.20-6.01)	0.920		
3A	0	0.999		
3B	1.11 (0.19-6.49)	0.907		
3C	0.57 (0.07-4.64)	0.601		
Tumor size	1.10 (0.91-1.33)	0.311		
Pelvic inlet area-CT (mm^2)	1 (1-1)	0.913		
Amount of dissected lymph node	0.970 (0.91-1.03)	0.348		
PCI	0.71 (0.52-1.01)	0.056		

For the gender variable, the 'female' category; for tumor localization, the 'upper rectum' category; for the type of operation, the 'open low anterior' category; for tumor stage, the 'stage 0' category; for fecal diversion, the 'present' category; for readmission, the 'absent' category; and for pelvic infection, the 'present' category were considered as the reference categories. ASA: American Society of Anesthesiologists; CT: Computed tomography; BMI: Body mass index; PCI: Pelvic cavity index.

CONCLUSION

This retrospective analysis explored the impact of pelvimetric assessments using both CT and MRI on surgical morbidity and local recurrence after rectal cancer surgery. Our findings demonstrate that a narrow pelvic structure, as indicated by a low PCI, is significantly positively correlated with surgical morbidity. However, contrary to our expectations, having a narrow or wide pelvic structure did not show a statistically significant impact on surgical outcomes such as operation time, estimated blood loss, or local recurrence within the first year postoperatively. These results suggest that while pelvimetry may be valuable in predicting surgical difficulty and morbidity, it may not be sufficient to predict local recurrence. In our study, we uniquely utilized both CT and MRI techniques for pelvic anatomy evaluation, providing a combination of two-dimensional and three-dimensional analyses. This approach offers a more comprehensive assessment of the pelvic anatomy than most existing studies, which typically rely on either CT or MRI alone. By employing both modalities, we provided a broader perspective in the context of surgical planning. In conclusion, pelvimetry could be a helpful tool for surgical risk stratification and for improving surgeon-patient communication, particularly in cases involving a complex pelvic anatomy. However, its limited role in predicting cancer recurrence underscores the importance of integrating other patient- and tumor-related factors. Large-scale, multicenter, and prospective studies are necessary to explore its clinical value and establish its broader applicability. Moreover, exploring the potential of combining pelvimetric data with other predictive markers may enhance surgical planning and improve both short- and long-term outcomes in rectal cancer patients.

Table 8 Risk factors affecting early recurrence development, regression analysis

	Univariate logistic regression model		Multivariate logistic regression model	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (years)	1.04 (0.99-1.09)	0.134		
Gender (male)	1.44 (0.45-4.62)	0.542		
BMI	0.99 (0.87-1.12)	0.854		
Tumor localization (upper rectum)		0.770		
Middle rectum	1.67 (0.37-7.48)	0.501		
Lower rectum	1.06 (0.29-3.95)	0.929		
ASA score	1.29 (0.44-3.78)	0.639		
Operation type (open low anterior)		0.721		
Laparoscopic low anterior	1.62 (0.51-55.17)	0.419		
Miles	0	0.999		
Operation duration	0.99 (0.98-1)	0.067	0.99 (0.97-0.99)	0.039
Blood loss (cc)	1 (0.99-1.02)	0.548		
Tumor stage (0)		0.807		
1	5.33 (0.34-82.83)	0.232		
2A	2 (0.19-20.97)	0.563		
2B	1.85 (0.16-20.94)	0.621		
3A	0	0.999		
3B	1.46 (0.11-18.96)	0.775		
3C	4.80 (0.39-59.90)	0.223		
Tumor size	0.94 (0.74-1.20)	0.635		
Pelvic inlet area-CT (mm^2)	1 (1-1)	0.900		
Amount of dissected lymph node	0.95 (0.88-1.03)	0.239		
PCI	1.02 (0.732-1.43)	0.894		
Length of stay	1.03 (0.94-1.12)	0.503		
Re-admission (exist)	3.63 (1.04-12.72)	0.044	6.07 (1.42-25.97)	0.015
Pelvic infection (exist)	2.25 (0.49-10.29)	0.296		

For the gender variable, the 'male' category; for tumor localization, the 'upper rectum' category; for the type of operation, the 'open Low anterior' category; for tumor stage, the 'stage 0' category; for readmission, the 'absent' category; and for pelvic infection, the 'absent' category were considered as the reference categories. ASA: American Society of Anesthesiologists; CT: Computed tomography; BMI: Body mass index; PCI: Pelvic cavity index.

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FOOTNOTES

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Data sharing statement: If the requesting individual contacted the corresponding author *via* email, the datasets used in our study, with the exception of the personal private data of the patients, could be shared.

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ORIGINAL ARTICLE

Clinical Trials Study

Novel multimodal analgesic regimen for perioperative pain management after hepatic artery infusion chemotherapy in patients with advanced hepatocellular carcinoma

Jing Yan, Rui An, Jing-Jing Wang, Min Wang, Qi Zhao, Shen Zhao, Jian Xu

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Abstract

BACKGROUND

Hepatic artery infusion chemotherapy (HAIC) is a widely used local therapeutic approach for intermediate to advanced-stage hepatocellular carcinoma (HCC), exhibiting considerable efficacy. However, the prevalence of postoperative pain highlights the importance of pain management. Owing to the limitations inherent in existing pain management strategies, this study investigates and assesses the analgesic effectiveness of a multimodal treatment protocol in mitigating pain after HAIC procedures.

AIM

To provide patients with a more comprehensive and effective pain management strategy.

METHODS

A total of 100 patients with primary HCC who underwent HAIC were randomly assigned to a control group (n = 50) and a multimodal group (n = 50). Baseline characteristics and perioperative data were collected. Upon enrollment, patients in the multimodal group received parecoxib (40 mg) 30 minutes before HAIC, followed by 48 hours of patient-controlled analgesia with sufentanil. In contrast, the control group underwent standard preoperative preparation (psychological support) and received dezocine (5 mg) intraoperatively, with intravenous flurbiprofen (100 mg) administered every 12 hours for 48 hours postoperatively.

RESULTS

Compared to the control group, the multimodal analgesia group exhibited

significantly lower resting and movement visual analog scale pain scores at postoperative 0, 2, 4, 6, and 12 hours ($P < 0.05$). Furthermore, the multimodal group experienced a reduced incidence of postoperative nausea and vomiting, as well as a lower overall frequency of adverse events, compared to the control group ($P < 0.05$). Patient satisfaction was also significantly higher in the multimodal group than in the control group ($P < 0.05$).

CONCLUSION

Our study demonstrates that multimodal analgesia is effective in reducing postoperative pain, minimizing adverse reactions, and improving patient satisfaction in HCC patients undergoing HAIC. This approach provides valuable clinical strategies for optimizing pain management in this patient population.

Key Words: Advanced hepatocellular carcinoma; Hepatic artery infusion chemotherapy; Multimodal analgesia regimen; Postoperative pain; Pain improvement

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Core Tip: Multimodal analgesia is an approach that combines different analgesic medications and techniques to target multiple pain pathways, enhancing pain relief while minimizing adverse effects. This study investigates the effectiveness of a multimodal regimen in managing pain after hepatic artery infusion chemotherapy procedures.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a prevalent malignant neoplasm worldwide, characterized by high incidence and mortality rates. It ranks third in cancer-related mortality globally[1]. HCC often presents insidiously, leading to most patients being diagnosed at the middle or advanced stage, missing the optimal window for surgical intervention[2]. Diagnosis of middle- and late-stage HCC primarily involves clinical symptoms, imaging examinations, and histopathological analysis[3]. Clinical symptoms, including severe abdominal pain, right flank pain, jaundice, and weight loss, are crucial indicators for initial evaluation[4,5]. Imaging methods, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), can assess tumor size, lesion extent, and the presence of lymph nodes or distant metastasis, thereby aiding in determining the disease stage[6,7].

In advanced HCC, surgical resection is typically not the preferred initial treatment modality. This is attributed to the high prevalence of tumor spread or extrahepatic metastases, which make surgery technically demanding and hazardous [8]. Therefore, non-surgical therapies, such as chemotherapy, radiation therapy, targeted therapy, and immunotherapy, have become the primary treatment approaches[9].

Hepatic artery infusion chemotherapy (HAIC) is a localized chemotherapy approach for liver malignancies, particularly primary HCC, where high concentrations of chemotherapeutic drugs are directly infused into the hepatic artery, leveraging the fact that liver tumors are predominantly supplied by the hepatic artery. Following decades of ongoing research and development, HAIC technology has achieved considerable progress in clinical applications[10]. Moreover, the combination of HAIC with other therapeutic modalities (*e.g.*, targeted therapies and immunotherapies) has amplified its efficacy, leading to enhanced patient outcomes and improved quality of life[11]. While HAIC offers advantages in the treatment of HCC, such as increased local drug concentration and reduced systemic toxicity and side effects, it has potential complications. These include hemorrhage, arterial rupture, nausea and vomiting, and bone marrow suppression. Among these, pain is a particularly considerable concern. During HAIC therapy, a substantial proportion of patients (approximately 64.6%) experience varying degrees of pain, which can considerably impair their quality of life and potentially contribute to reduced survival duration[12].

Pain management is an essential component of the perioperative period of HAIC for HCC[13]. Traditional single-mode analgesia, such as the exclusive use of opioids, can provide pain relief but often leads to adverse effects such as respiratory depression, nausea, vomiting, constipation, and addiction[14,15]. In recent years, with the evolution of pain management concepts and advancements in analgesic techniques, there has been growing attention to multimodal analgesia schemes[16]. Multimodal analgesia, also known as balanced analgesia, combines different analgesic drugs with different mechanisms of action and uses multiple analgesic methods to target various pain conduction pathways. This approach achieves a synergistic analgesic effect while minimizing adverse reactions and enhancing pain relief[17]. A coalition of 14 professional societies recently recommended multimodal analgesia, advocating for the combined use of various analgesics and techniques alongside nonpharmacologic interventions[18]. Pain is a complex, multifactorial phenomenon that requires multimodal analgesic regimens, using combinations of analgesics with diverse mechanisms of

action and/or different administration routes. Such strategies have demonstrated improved postoperative pain relief and reduced opioid consumption, thereby minimizing opioid-related adverse events[19,20]. Consequently, the implementation of multimodal analgesia in the perioperative period of HAIC can not only effectively alleviate treatment-related pain but also reduce the dosage of individual analgesic medications and lower the incidence of adverse reactions. This ultimately enhances patients' treatment experience and compliance. More specifically, the multimodal analgesia regimen may incorporate the prophylactic administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX-2) inhibitors preoperatively, the use of local anesthesia or regional nerve blocks intraoperatively, and the postoperative combined application of opioids and analgesic pumps[21].

Despite the known benefits of multimodal analgesia, it is deemed unsuitable for routine clinical practice[22]. An analysis of 315 hospital administrative databases involving approximately 800000 patients undergoing four common major surgical procedures (open lobectomy, open colectomy, total knee replacement, and below-knee amputation) revealed considerable variations in the utilization of multimodal analgesia[23]. Analgesic combinations are frequently irrational, and multimodal protocols often fail to address different types of pain responses (*e.g.*, nociceptive and inflammatory pain)[24,25]. Currently, there are few or insufficient studies on perioperative pain relief in HAIC. Consequently, there is a lack of strong evidence supporting the implementation of multimodal analgesic programs. This knowledge gap hinders our comprehensive understanding and widespread application of multimodal analgesia in patients with HCC undergoing HAIC. Therefore, this study aims to address the pain management challenges faced by HCC patients receiving HAIC by introducing multimodal analgesia. Our aim is to investigate more effective and safer pain management approaches and contribute novel insights to the development of comprehensive treatment strategies for HCC patients.

MATERIALS AND METHODS

Patients

A total of 100 patients undergoing HAIC surgery for primary HCC at Xijing Hospital, The Fourth Military Medical University from January to December 2023 were included based on standard criteria. All patients were diagnosed with primary HCC through pathology, imaging, clinical symptoms, and laboratory examinations.

To maintain the objectivity and neutrality of the research findings, a randomized approach was used to assign patients to groups using a random number table. The procedure involved assigning a distinct identification number to each of the 100 cases of postoperative patients with primary liver cancer undergoing HAIC. Subsequently, a computer-generated random number table was used to randomly allocate the patients into two groups: The control group (n = 50) and the multimodal group (n = 50). The objective of randomization was to mitigate or eliminate possible selection biases and to guarantee that the baseline characteristics of the two patient groups were closely aligned, thereby facilitating an accurate evaluation of the impact of multimodal treatment on pain management after HAIC.

Measures to ensure the reliability of double-blind assessment

(1) In this study, the double-blind principle indicates that both the researchers performing the assessments (including data analysts) and the patients receiving treatment were unaware of group assignments. To maintain this confidentiality, all treatment-related information, such as group labels and treatment regimens, was concealed or encrypted during the data collection and analysis phases. Data were independently collected by investigators who were not involved in determining treatment assignments to reduce the potential for bias. Statistical analysis was performed in a blinded manner, with data analysts processing the data and analyzing results without knowledge of group assignments; and (2) A dedicated quality control team was established during the study to oversee the entire process, including randomization, data collection, and evaluation, ensuring that all procedures adhered to the study protocol and upheld the double-blind principle.

This study was approved by the Medical Ethics Committee of the hospital (document number: KY20232191-F-1), and all patients signed informed consent.

Diagnostic criteria: The diagnostic criteria for patients with primary HCC are based on the Diagnostic Guidelines for Primary HCC[26]. A clinical diagnosis of HCC can be established when the following conditions are simultaneously met: Either condition (1) + (2)a or condition (1) + (2)b + (3). The criteria are as follows: (1) Evidence of cirrhosis along with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection, indicated by positive HBV and/or HCV antigen status; (2) Typical HCC imaging characteristics observed on contemporaneous multi-detector CT scans and/or dynamic contrast-enhanced MRI, showing rapid and heterogeneous vascular enhancement of the liver mass during the arterial phase (arterial hypervascularity), followed by rapid washout in the venous or delayed phase (venous or delayed phase washout). If the liver mass diameter is ≥ 2 cm, the presence of the abovementioned HCC characteristics in either CT or MRI is sufficient for diagnosing HCC; if the liver mass diameter is 1-2 cm, both CT and MRI must display the abovementioned HCC characteristics for a definitive diagnosis, enhancing diagnostic specificity; and (3) Serum alpha fetoprotein (AFP) levels ≥ 400 μg/L sustained for one month or ≥ 200 μg/L sustained for two months, with other causes of AFP elevation excluded, including pregnancy, germ cell tumors of the reproductive system, active liver diseases, and secondary liver cancers.

Inclusion criteria[27]: (1) Chinese Liver Cancer Staging Scheme (CNLC) stages IIb, IIIa, IIIb; (2) Adjuvant HAIC post-HCC resection to prevent recurrence; (3) Locally advanced liver cancer with good liver function (Child-Pugh grade A or

B) suitable for conversion therapy; (4) Combined radiotherapy for HCC with portal vein thrombus to achieve a higher conversion rate; (5) Locally advanced intrahepatic and hilar cholangiocarcinoma; and (6) Inoperable liver metastases originating from colorectal and gastric cancer.

Exclusion criteria[27]: (1) Severe liver dysfunction (Child-Pugh grade C), along with obvious jaundice, hepatic encephalopathy, refractory abdominal fluid, or hepatorenal syndrome; (2) Severely decreased coagulation function that cannot be corrected; (3) Presence of active hepatitis or severe infection that cannot be treated simultaneously; (4) Extensive distant metastasis of the tumor with an estimated survival time of less than 3 months; (5) Cachexia or multiple organ failure; (6) Substantially reduced peripheral blood white blood cell (WBC) count and platelet (PLT) count, specifically WBC < 3.0×10^9/L (note: This is a non-absolute contraindication because WBC reduction in hypersplenism differs from chemotherapy) and PLT < 60×10^9/L; and (7) Renal dysfunction indicated by creatinine levels > 176.8 μmol/L (2 mg/dL) or creatinine clearance < 30 mL/min.

Analgesic regimen

To ensure the continuity and effectiveness of the analgesic regimen, the same team of anesthesiologists, who were familiar with the patient's condition and specific analgesic plan, administered anesthesia.

Control group: The control group received standard preoperative preparation, which included psychological support, and was given 5 mg of dezocine during HAIC. After the treatment, flurbiprofen 100 mg was intravenously infused every 12 hours over a 48-hour period. If the patient's resting visual analog scale (VAS) pain score exceeded 3, tramadol 100 mg or an equivalent opioid was administered intravenously.

Multimodal group: In the multimodal group, patients received an intravenous injection of 40 mg parecoxib sodium 30 minutes prior to the start of HAIC, while the patient-controlled analgesia (PCA) pump was activated simultaneously with the initiation of HAIC. This consisted of sufentanil (100 μg) and dexmedetomidine (200 μg), diluted with a 0.9% saline solution to a total volume of 100 mL. The initial dose was set at 2 mL, with an on-demand push also at 2 mL and a lockout interval of 5 minutes. The infusion rate was 2 mL/h, decreasing to 0 mL/h after surgery. If the patient's resting VAS pain score averaged over two assessments was greater than 3, the background infusion rate was increased to 1 mL/h. PCA was available for use in 48 minutes after surgery (Figure 1).

HAIC surgery

HAIC was performed by the same team of doctors using the Seldinger technique for arterial catheterization[28]. During the procedure, angiography of the celiac trunk and superior mesenteric artery was performed to identify the blood supply arteries of the tumor. Additional angiography of other arteries was performed as needed for a comprehensive evaluation. The catheter was then advanced in a selective manner to reach the main feeding artery of the tumor, after which the non-primary feeding arteries were addressed. Chemotherapy drugs were administered through the catheter, with a heparin solution used during the procedure to prevent catheter occlusion. The exposed portion of the catheter was secured and protected. During chemotherapy, the patient remained in bed, avoiding bending or exerting force on the catheterized limb. Upon completion of chemotherapy, the catheter was removed, and the puncture site was compressed and dressed. The patient was allowed to ambulate once the bleeding had stopped.

Data collection

Patient demographics, including age, gender, Child-Pugh classification, history of HAIC, lifestyle-related challenges, prior liver conditions, and complications, were documented. Additionally, perioperative information, such as the duration of HAIC treatment and length of the post-HAIC hospital stay, was recorded.

The evaluation of patients' VAS scores at rest and during exercise[29] was performed at the following time points: Preoperative, intraoperative, and postoperative at 1 hour (T0), 2 hours (T2), 4 hours (T4), 6 hours, 12 hours (T12), 24 hours (T24), and 48 hours (T48).

Patient satisfaction[30] was recorded 48 hours after surgery, using a five-point scale: 1 is "very bad," 2 is "bad," 3 is "moderate," 4 is "good," and 5 is "very good."

The sedation score[31] was assessed 48 hours after surgery. The scoring system was as follows: 0 is "awake," 1 is "mildly sedate," 2 is "inclined to sleep," and 3 is "deep sleep, unable to wake up."

Additionally, postoperative adverse drug reactions were recorded in a 48-hour period, including symptoms such as nausea, vomiting, constipation, difficulty urinating, fatigue, bradycardia (slow heart rate), hypotension (low blood pressure), and respiratory depression.

Statistical analysis

Statistical analyses were performed using SPSS version 27.0 (SPSS Inc., Chicago, IL, United States). Patient characteristics and perioperative data were compared between the two groups using *t*-tests, Fischer's exact test, and χ^2 tests for categorical variables. Time-course changes in pain scores were compared using *t*-tests. Bar graphs comparing the VAS pain scores of the two groups were generated using GraphPad Prism 9.5 software. The distribution of percentages, patient satisfaction levels, and adverse drug reactions were analyzed using Fisher's exact test or χ^2 tests. All results are presented as mean ± SD and patient counts (%), with statistical significance set at $P < 0.05$.

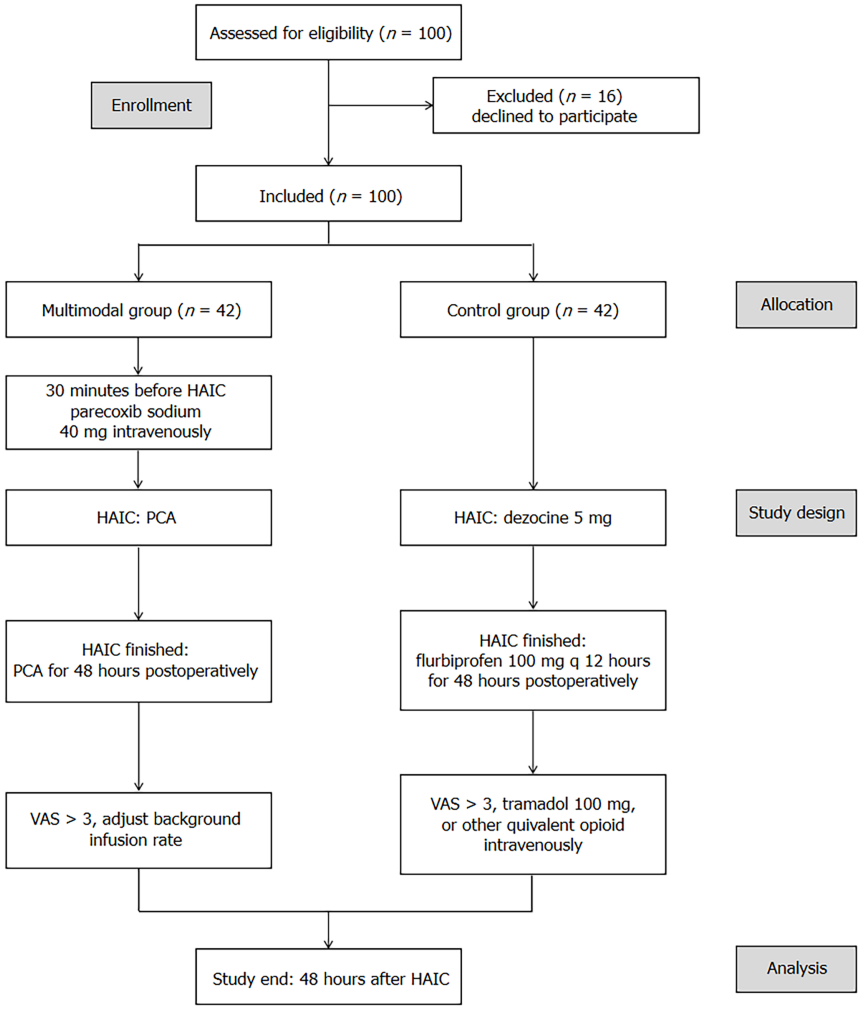


Figure 1 Flowchart exhibiting course of the study. HAIC: Hepatic artery infusion chemotherapy; PCA: Patient-controlled analgesia; VAS: Visual analog scale.

RESULTS

Comparison of general and perioperative data between the two groups

After applying the patient grouping and selection criteria for this study, no patients were excluded from the analysis (Figure 1). There were no statistically significant differences in age, sex, Child-Pugh grade, history of HAIC, adverse life history, liver disease history, or comorbidities between the two groups. Consequently, no significant differences in baseline characteristics were observed between the control group (n = 50) and the multimodal group (n = 50) (P > 0.05). During the perioperative period, no significant differences were found in the duration of HAIC (t = 0.425, P = 0.809) or the length of hospital stay after HAIC (t = 0.839, P = 0.403) between the two groups. Detailed information is provided in Table 1.

VAS pain score

As shown in Table 2 and Figure 2, the baseline VAS pain scores measured 1 hour before (t = 0.358, P = 0.721) and during HAIC (t = 0.775, P = 0.440) showed no statistically significant differences between the two groups (Figure 2, Table 2). However, significant differences in VAS pain scores at rest and during movement were observed at various time points after HAIC: 0 hour (rest: T = 8.667, P = 0.001; movement: T = 8.733, P = 0.001), 2 hours (rest: T = 5.040, P = 0.006; movement: T = 3.133, P = 0.002), 4 hours (rest: T = 6.928, P = 0.001; movement: T = 6.928, P = 0.001), 6 hours (rest: T = 0.640, P = 0.001; movement: T = 6.640, P = 0.001), and 12 hours (rest: T = 8.883, P = 0.001; movement: T = 7.310, P = 0.001). In contrast, no statistically significant differences were observed in VAS pain scores between resting and movement at 24 hours (rest: T = 1.939, P = 0.055; movement: T = 0.165, P = 0.869) and 48 hours after HAIC (rest: T = 1.497, P = 0.458; movement: T = 0.503, P = 0.616).

Comparison of patient satisfaction between the two groups 48 hours after surgery

The findings revealed that patient satisfaction levels, assessed 48 hours post-surgery, were significantly higher in the multimodal group compared to the control group (χ^2 = 11.753, P = 0.008). Specifically, in the control group, 20% of patients reported "excellent" satisfaction, 44% reported "good," 30% reported "moderate," and 6% reported "poor." In

Table 1 Comparison of general and perioperative data between the two groups, *n* (%)

Classification	Control group	Multimodal group	t/χ^2	*P* value
Cases	50	50		
Age	55.10 ± 8.61	52.00 ± 9.74	1.686	0.095
Gender			0.378	0.539
Male	29 (58)	32 (64)		
Female	21 (42)	18 (36)		
Child-Pugh class			0.367	0.545
A	27 (54)	30 (60)		
B	23 (46)	20 (40)		
History of HAIC			0.161	0.688
First time	26 (52)	28 (56)		
Twice or more	24 (48)	22 (44)		
Adverse life history			0.174	0.677
No	19 (38)	17 (34)		
Yes	31 (62)	33 (66)		
History of liver disease			0.178	0.673
No	16 (32)	18 (36)		
Yes	34 (68)	32 (64)		
Complication			0.198	0.656
No	13 (26)	15 (30)		
Yes	37 (74)	35 (70)		
Duration of HAIC (min)			0.425	0.809
< 30 minutes	32 (64)	35 (70)		
30-60 minutes	17 (34)	14 (28)		
> 60 minutes	1 (2)	1 (2)		
Duration of hospital stay after (day)	3.78 ± 1.87	3.48 ± 1.71	0.839	0.403

HAIC: Hepatic artery infusion chemotherapy.

contrast, in the multimodal group, 50% of patients reported "excellent" satisfaction, 30% reported "good," and 20% reported "moderate." Refer to Table 3 for detailed information.

Comparison of adverse reactions between the two groups

Compared to the control group, the multimodal group exhibited significantly lower incidences of postoperative nausea and vomiting (PONV) ($\chi^2 = 4.882$, $P = 0.027$) and total adverse reactions ($\chi^2 = 10.306$, $P = 0.001$). At 48 h post-surgery, the control group experienced adverse reactions including PONV ($n = 15$), constipation ($n = 7$), dysuria ($n = 6$), and hypersomnia ($n = 10$), while the multimodal group reported reduced incidences with PONV ($n = 6$), constipation ($n = 4$), dysuria ($n = 4$), and hypersomnia ($n = 5$). Refer to Table 4 for detailed information.

DISCUSSION

This study has emphasized the substantial advantages of using a multimodal analgesia regimen in managing postoperative pain after HAIC for advanced-stage HCC. Our findings demonstrated that, in comparison to conventional analgesia, the multimodal analgesia regimen was more effective in alleviating pain, minimizing side effects, and enhancing patient satisfaction.

Pain continues to pose a considerable global health challenge. For many years, μ-opioid receptor agonists and NSAIDs have been the primary modalities relied upon by clinicians for pain management[32]. While μ-opioid receptor agonists are effective in pain relief, their associated adverse effects are substantial, often leading physicians to adjust treatment

Table 2 Compared two groups of visual analog scale pain score

	Time point	Control group (*n* = 50)	Multimodal group (*n* = 50)	*t*	*P* value
Rest	1 hour before HAIC	0.58 ± 0.57	0.54 ± 0.54	0.358	0.721
	During the HAIC	0.38 ± 0.49	0.46 ± 0.54	0.775	0.440
	T0	1.5 ± 0.58	0.56 ± 0.50	8.667	0.001
	T2	1.8 ± 0.73	1.14 ± 0.57	5.040	0.006
	T4	1.88 ± 0.77	0.96 ± 0.53	6.928	0.001
	T6	1.78 ± 0.51	0.98 ± 0.68	6.640	0.001
	T12	1.62 ± 0.49	0.7 ± 0.54	8.883	0.001
	T24	0.56 ± 0.58	0.34 ± 0.56	1.939	0.055
	T48	0.52 ± 0.58	0.36 ± 0.48	1.497	0.138
Movement	1 hour before HAIC	0.7 ± 0.54	0.62 ± 0.53	0.745	0.458
	During the HAIC	0.5 ± 0.51	0.62 ± 0.60	-1.079	0.283
	T0	1.68 ± 0.51	0.8 ± 0.49	8.733	0.001
	T2	1.9 ± 0.89	1.44 ± 0.54	3.133	0.002
	T4	1.94 ± 0.77	1.58 ± 0.50	6.928	0.001
	T6	1.96 ± 0.45	0.96 ± 0.53	6.640	0.001
	T12	1.64 ± 0.69	0.74 ± 0.53	7.310	0.001
	T24	0.84 ± 0.47	0.82 ± 0.72	0.165	0.869
	T48	0.52 ± 0.58	0.46 ± 0.61	0.503	0.616

HAIC: Hepatic artery infusion chemotherapy.

Table 3 Comparison of patient satisfaction between the two groups 48 hours after surgery, *n* (%)

	Cases (*n*)	1 = very bad	2 = bad	3 = moderate	4 = good	5 = very good	χ^2	*P* value
Control group	50	0 (0)	3 (6)	15 (30)	22 (44)	10 (20)	11.753	0.008
Multimodal group	50	0 (0)	0 (0%)	10 (20)	15 (30)	25 (50)		

Table 4 Comparison of adverse reactions between the two groups, *n* (%)

Adverse reactions	Control group (*n* = 50)	Multimodal group (*n* = 50)	χ^2	*P* value
PONV	15 (30)	6 (12)	4.882	0.027
Constipation	7 (14)	4 (8)	0.919	0.338
Dysuria	6 (12)	4 (8)	0.444	0.505
Hypersomnia	10 (20)	5 (10)	1.961	0.161
Total	33 (66)	19 (38)	10.306	0.001

PONV: Postoperative nausea and vomiting.

regimens or even discontinue medication, making it difficult to adequately control pain[33]. Currently, the serious issue of opioid abuse has further exacerbated the need for safer and more effective analgesic solutions.

The findings of this study demonstrated that the multimodal group exhibited superior analgesic efficacy compared to the control group. It is hypothesized that the combination of an NSAID (parecoxib sodium) and an opioid (sufentanil) in the multimodal group produces a synergistic effect, enhancing analgesia and potentially reducing the dosage of each drug, thereby minimizing adverse effects. Additionally, the adjunctive use of an α2-adrenergic receptor agonist (dexmedetomidine) further enhances analgesia while providing improved sedation and comfort. Parecoxib sodium, a

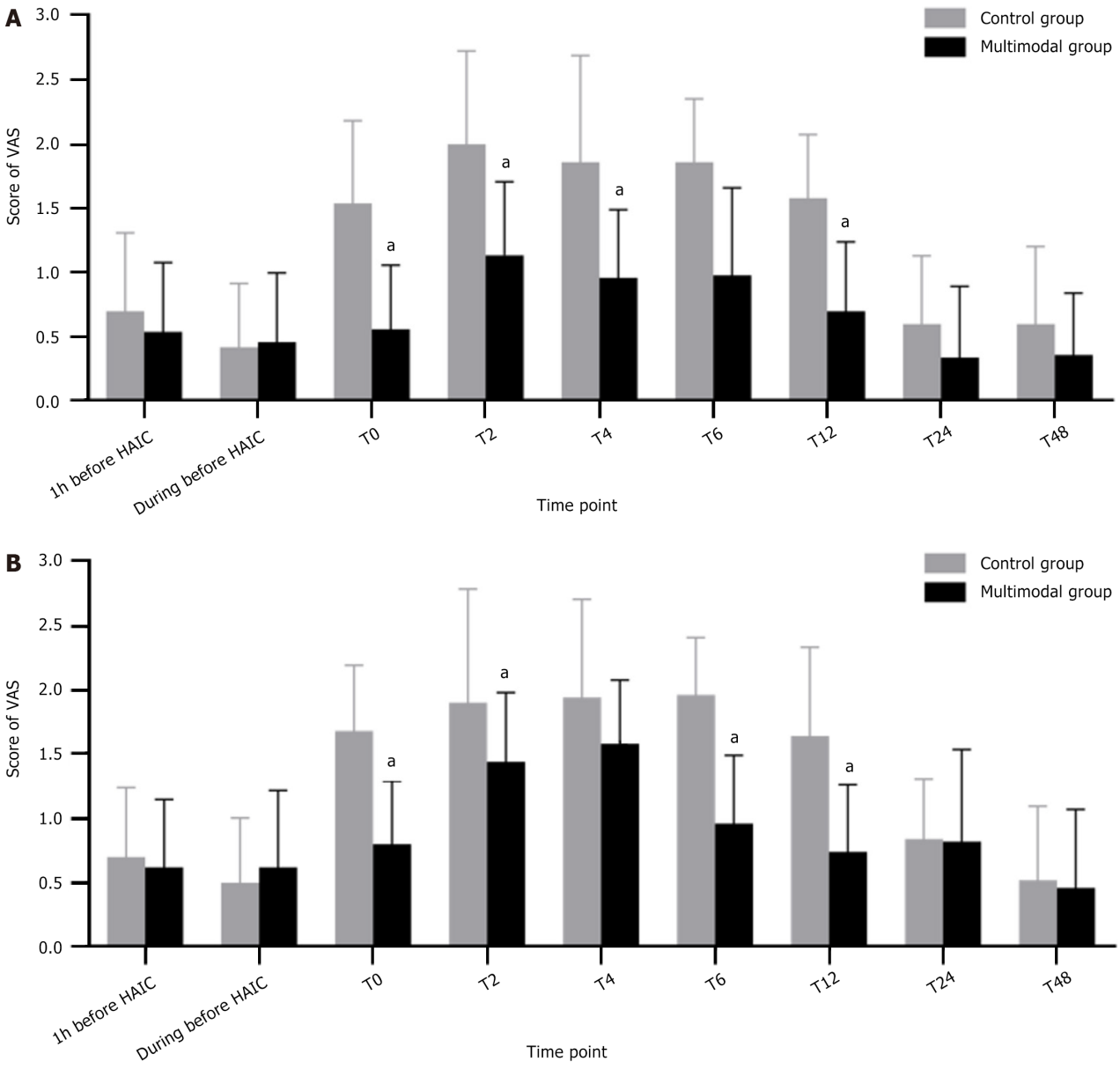


Figure 2 Visual analog scale scores of the control group and the multimodal group at different time points. A: Score at rest; B: Score at movement. [a]*P* < 0.05 *vs* control group. VAS: Visual analog scale.

prodrug of an NSAID, exerts its effects after conversion to valdecoxib in the body. By inhibiting the activity of COX-2, parecoxib sodium reduces prostaglandin synthesis and is commonly used in perioperative pain management[34]. The combined use of parecoxib sodium and opioids in the multimodal analgesia approach has been shown to be a more effective pain management strategy than relying solely on opioids[35]. This combined therapy not only considerably reduces the intensity of postoperative pain but also effectively decreases opioid dependence and overall consumption [36]. Studies have demonstrated that a multimodal analgesia regimen incorporating parecoxib and sufentanil improves postoperative pain management in HCC patients undergoing transarterial chemoembolization (TACE)[37]. Therefore, the positive effects demonstrated by the multimodal analgesia regimen in this study align with previous findings that have used the same analgesic strategy in various surgical settings. This observation further confirms the broad effectiveness and superiority of this analgesic strategy for all surgical procedures. Despite variations in surgical types among the participants, the analgesic regimen's core components-the synergistic activity of a NSAID (parecoxib sodium) with an opioid (sufentanil) and the adjunct effect of an α2-adrenergic receptor agonist (dexmedetomidine)-remained unchanged [38]. Both additives considerably enhanced the analgesic effect, potentially enabling lower drug doses and reducing adverse reactions. This points to an improved postoperative pain management strategy and a better patient experience. This finding solidifies the role of multimodal analgesia in clinical practice while also providing robust support for future pain management strategies.

This study demonstrated that the multimodal analgesia group experienced considerably lower VAS pain scores at various postoperative time points (0, 2, 4, 6, and 12 hours, both at rest and during movement) compared to the control group. These findings highlight the effectiveness of the multimodal analgesia protocol in providing substantial pain relief. Conventional analgesic medications frequently fall short of adequately managing pain related to HAIC, hindering

effective pain control. While high-dose potent opioids can provide analgesia, they may be associated with serious complications, such as respiratory depression, restricting their clinical use[39]. Lidocaine, previously used as a local anesthetic and for treating cardiac arrhythmias, has recently attracted attention among researchers for its application during arterial chemoembolization procedures, demonstrating its substantial analgesic properties[12]. Studies have shown that using lidocaine during arterial chemoembolization can reduce the incidence and severity of pain after surgery [40]. Moreover, Wu *et al*[12] reported that lidocaine was effective in 96% (361/376) of patients undergoing HAIC, resulting in an 85.6% reduction in VAS scores. This is particularly crucial for HAIC patients because uncontrolled pain can hinder their recovery and overall well-being. By alleviating pain, the multimodal analgesia regimen can contribute to a better recovery experience and improved patient outcomes.

The findings of this study demonstrated that the overall incidence of PONV and the total rate of adverse reactions were considerably lower in the multimodal group compared to the control group, highlighting the safety of this analgesia regimen. PONV is a common and distressing postoperative complication, and it can lead to delayed patient discharge, prolonged recovery, and increased healthcare expenses[41]. During the perioperative period, patients may experience frequent vomiting, making it difficult for oral medications to be absorbed effectively or maintain adequate blood concentrations, which can impact analgesia efficacy[42]. Moreover, patients who rely on opioids for chronic pain management often experience a range of adverse effects, including mild and manageable symptoms such as nausea, vomiting, sedation, and urinary retention, as well as more severe and complex health issues such as increased drug dependence, refractory constipation, and the potential risk of drug addiction[43]. Despite efforts to address PONV, its high incidence persists[44]. Therefore, reducing PONV is essential for patient comfort and early mobilization.

Furthermore, the findings of this study demonstrated a substantially higher level of patient satisfaction in the multimodal analgesia group compared to the conventional group, highlighting the importance of multimodal pain management strategies in improving patient outcomes. By effectively alleviating pain and minimizing adverse reactions, the multimodal analgesia regimen provided a more positive experience for patients. Research has also shown that a multimodal analgesia regimen incorporating parecoxib and sufentanil resulted in higher patient satisfaction in HCC patients undergoing TACE compared to the control group[37], further validating its clinical superiority. Therefore, it is evident that multimodal analgesia, compared to single-mode pain management methods, not only effectively reduces patients' pain but also substantially decreases the incidence of adverse reactions, ultimately leading to a more comfortable and positive treatment experience for patients.

This study offers valuable insights into optimal pain management strategies after HAIC. The multimodal analgesia regimen presented can serve as a model for developing evidence-based guidelines for pain management in this patient population. However, we acknowledge several limitations. While this study provided insights into multimodal analgesia for pain management after HAIC treatment of advanced HCC, the assessment of pain and satisfaction levels was inherently subjective, relying on self-reported descriptions from individuals. Additionally, the study was limited in duration and did not address the long-term recovery effects. Additionally, the sample size of the study was relatively small, which may limit the generalizability of the results. Larger studies are needed to validate the current findings. The multimodal analgesic regimen, which included preemptive multimodal analgesia in this study, may differ from those applied at other medical centers or in different regions. Variations in multimodal pain regimens could influence the results. Additionally, only cases undergoing HAIC were included. Thus, the findings cannot be generalized to cases treated with other surgical procedures.

CONCLUSION

In summary, this study underscored the therapeutic importance of a multimodal analgesia approach in effectively managing postoperative pain in patients undergoing HAIC for advanced-stage HCC. By providing effective pain relief, minimizing adverse reactions, and enhancing patient satisfaction, this regimen represents a considerable advancement in cancer-related pain management, leading to improved patient outcomes and quality of life. It offers the HCC treatment team a practical and feasible pain management regimen, facilitating more individualized and accurate pain control. By promoting the concept of multimodal analgesia, healthcare institutions can improve their existing pain management protocols, strengthen interdisciplinary collaboration, and provide patients with more comprehensive and effective pain management services. This not only enhances patients' treatment experience and satisfaction but also expedites postoperative recovery, reduces the occurrence of complications, and ultimately improves patients' prognosis and well-being. This study has important implications for guiding future pain management strategies in similar surgical procedures. It encourages clinicians to fully consider the complexity of pain management during surgical planning and postoperative care, actively incorporating multimodal analgesia regimens to achieve comprehensive pain control. As multimodal analgesia regimens are applied and validated across more surgical fields, they are likely to emerge as a pivotal trend in future pain management, contributing to an overall improvement in the quality of medical care.

FOOTNOTES

Author contributions: Yan J and An R designed the research and wrote the first manuscript; Yan J, An R, Xu J, Wang JJ, Wang M, Zhao Q and Zhao S contributed to conceiving the research and analyzing data; Yan J and An R conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript. Yan J and An R contributed equally to this work as co-first authors.

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ORIGINAL ARTICLE

Observational Study

Relationship between peripheral blood endotoxin, toll-like receptor 4 expression, and postoperative infection following surgery for acute appendicitis

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Abstract

BACKGROUND

Acute appendicitis, a common condition with a higher prevalence among men, has shown an increasing incidence in recent years owing to lifestyle changes. It is characterized by right lower quadrant abdominal pain, rebound tenderness, and rapid onset. Its pathogenesis is complex and potentially linked to infection, environment, and genetics. Timely intervention is crucial to prevent complications. While surgery is the primary treatment, it carries risks, including postoperative infections that may necessitate re-operation. Gram-negative bacteria release endotoxin (ETX), which induces inflammation and is recognized by toll-like receptor 4 (TLR4). This study evaluated ETX and TLR4 levels in patients with acute appendicitis to assess the risk of postoperative incision infections, aiding in prevention and treatment.

AIM
To explore ETX and TLR4 expression in the blood of patients with acute appendicitis and its association with in postoperative incision infection.

METHODS
A total of 153 patients with acute appendicitis treated at our hospital between April 2022 and March 2024 (n = 153) were included in the study. Patients were categorized into infected (n = 36) and uninfected (n = 117) groups according to the development of postoperative incision infections. General characteristics and blood levels of ETX and TLR4 were compared, and the factors influencing postoperative infection were identified using multivariate logistic regression. ETX and TLR4 predictive values were analyzed using receiver operating characteristic curves.

RESULTS
No statistically significant differences were observed between the two groups in terms of sex, age, or other general characteristics (P > 0.05). Compared to the uninfected group, the infected group had a higher proportion of patients with suppurative or gangrenous appendicitis, longer surgical times, longer incision lengths, and elevated ETX and TLR4 levels (P < 0.05). Multivariate logistic regression analysis identified pathological type, surgical method, surgical time, and incision length as factors influencing postoperative incision infection in acute appendicitis. Receiver operating characteristic curve analysis revealed that both ETX and TLR4 levels were predictive factors for postoperative incision infection, with higher prediction efficiency when combined.

CONCLUSION
Pathological type, surgical method, surgical time, and incision length significantly influence postoperative incision infection risk in patients with acute appendicitis. Elevated ETX and TLR4 levels serve as valuable predictors of post-appendectomy infections.

Key Words: Acute appendicitis; Endotoxin; Toll-like receptor 4; Risk factors; Wound infection

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Core Tip: Clinical data from patients with acute appendicitis, with and without postoperative incision infections, were compared to analyze factors influencing incision infection. This study explored gram-negative bacteria release endotoxin and toll-like receptor 4 expression in the blood of patients with acute appendicitis, and identified reliable indicators for predicting postoperative incision infections. Pathological type, surgical method, surgical time, and incision length are significant factors influencing the postoperative incision infection risk.

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INTRODUCTION

Acute appendicitis is a common condition, ranking as the leading cause of acute abdomen and showing a higher incidence among men[1]. Changes in dietary and lifestyle habits associated with improved living standards have contributed to a rising incidence of acute appendicitis[2]. This condition is primarily characterized by right lower quadrant abdominal pain, tenderness at the appendiceal site, rebound tenderness, and rapid progression[3]. The pathogenesis of this disease is relatively complex, with multiple theories, and its etiology is believed to be related to factors such as infection, environmental factors, and genetic predisposition[4]. Prompt diagnosis and treatment are essential to prevent complications, such as systemic infections or diffuse peritonitis, which may arise from disease progression[5]. Surgery remains the primary treatment option for acute appendicitis. However, surgical resection carries a risk of incision infection, making it difficult for the wound to heal and even requiring a second surgery, which increases the physiological and psychological burden on patients[6]. Studies have shown that gram-negative bacteria are the main pathogens that cause surgical incision infections. Endotoxins (ETX) are one of the main components of gram-negative bacterial cell walls. Bacteria adhere to other cells and release ETX, leading to inflammatory reactions[7]. Toll-like receptor 4 (TLR4) recognizes heat shock proteins released from cells in the absence of cellular necrosis and lipopolysaccharides from gram-negative bacteria[8]. Changes in ETX and TLR4 expression may correlate with postoperative incision infections in patients with acute appendicitis. Therefore, this study examined patients with acute appendicitis admitted to our hospital and evaluated the ETX and TLR4 levels in postoperative incision infection to provide a basis for the early assessment of the risk of incision infection after appendectomy, and thereby the prevention and treatment of incision infection.

MATERIALS AND METHODS

Study subjects

A total of 153 patients with acute appendicitis who underwent surgical treatment at our hospital between April 2022 and March 2024 were selected. Patients were categorized into two groups based on the presence or absence of postoperative incision infections: Infected (n = 36) and the uninfected (n = 117). The inclusion criteria were as follows: (1) Patients who met the diagnostic criteria for acute appendicitis[9]; (2) Patients who successfully underwent appendectomy; (3) Patients without infectious diseases prior to the surgery; and (4) Patients who provided informed consent to participate in the study. The exclusion criteria were as follows: (1) History of other gastrointestinal surgeries within 3 months; (2) Presence of infectious diseases or abnormal coagulation function prior to surgery; (3) Coexisting mental or communication disorders; or (4) Diagnosis of autoimmune diseases. This study was approved by the Medical Ethics Committee of our hospital.

Clinical data

After admission, patients with acute appendicitis were anesthetized, incised, the appendix explored and removed, the root of the appendix treated, the abdominal cavity cleaned, and the incision sutured. Clinical data for all patients, including sex, age, pathological type, and surgical method (acute appendicitis with mild disease and small inflammatory range were treated by laparoscopic surgery, while traditional open surgery was used for acute appendicitis with severe disease, extensive inflammation or other complications), surgical time, incision length, underlying diseases, blood routine, C-reactive protein levels, and ETX and TLR4 levels detected within 24 hours after surgery, were collected. Briefly, 5 mL of fasting venous blood was collected from each patient, placed in an anticoagulant tube, stored at negative 4 °C, and centrifuged at 3000 r/minute for 15 minutes. The resulting supernatant was collected for enzyme linked immunosorbent assay for measurement of the ETX and TLR4 levels. The reagent kit was purchased from Shanghai Ruifan Biotechnology Co., Ltd. and the iMark enzyme linked immunosorbent assay reader was purchased from Bio-Rad (Hercules, CA, United States).

Criteria for determining incision infection

Incision infections were diagnosed based on the "diagnostic criteria for hospital infections (trial)"[10]. The following were assessed: (1) Superficial incision showed redness, burning, or purulent discharge, and bacterial culture showed positive results; (2) Pus appeared following deep incision puncture and drainage; (3) The wound naturally ruptured or was opened by a physician, with purulent discharge or local pain, with a body temperature of ≥ 38 °C; and (4) Further surgical exploration revealed the presence of a deep incision abscess through pathological tissue testing or imaging examination. If any of the above conditions were present, an incision infection was diagnosed.

Statistical analysis

The results were analyzed using the SPSS20.0 software. Measurement data is expressed as the mean ± SD and subjected to t-test. Quantitative data are represented as n (%), and χ^2-tests were performed. Factors influencing postoperative infection were identified using multivariate logistic regression, and the predictive value of the ETX and TLR4 levels in the peripheral blood of patients with postoperative infection was analyzed using receiver operating characteristic (ROC) curves. $P < 0.05$ indicated a statistically significant difference.

RESULTS

As shown in Table 1, 36 patients who developed postoperative infections were categorized into the infected group, while the remaining patients were assigned to the uninfected group. No statistically significant differences were observed between the two groups in terms of sex, age, or other factors ($P > 0.05$). Compared with the uninfected group, the infected group had a higher proportion of patients with purulent or gangrenous appendicitis, underwent traditional open surgery, and had longer surgical times and incision lengths ($P < 0.05$). The non-conditional logistic regression analysis of the risk factors for postoperative incision infection is summarized in Table 2. Using postoperative incision infection as the dependent variable and pathological type (uncomplicated = 0, suppurative or gangrenous = 1), surgical method (laparoscopic surgery = 0, traditional open surgery = 1), surgical time, and incision length as independent variables, multivariate unconditional logistic regression analysis was conducted. The pathological type, surgical method, surgical time, and incision length were factors that influenced postoperative incision infections in acute appendicitis. Laboratory data comparisons are presented in Table 3. The ETX and TLR4 levels in the infected group were found to be higher than in the uninfected group ($P < 0.05$). ROC curve analysis indicated that the area under the curve for evaluating postoperative incision infections in patients based on ETX and TLR4 levels were 0.841 and 0.769, respectively (Table 4, Figure 1). The area under the curve based on both ETX and TLR4 was 0.922, with a sensitivity and specificity of 86.11% and 85.54%, respectively.

Table 1 Comparison of general characteristics, mean ± SD or *n*

Index	Infected group (*n* = 36)	Uninfected group (*n* = 117)	t/χ^2	*P* value
Sex			0.224	0.636
Male	21	63		
Female	15	54		
Age, years	38.36 ± 7.19	39.01 ± 6.71	0.498	0.619
Pathological type[1]			7.136	0.008
Uncomplicated	2	31		
Purulent or gangrenous	34	86		
Operation method[1]			4.366	0.037
Traditional open surgery	34	93		
Laparoscopic surgery	2	24		
Surgery time, minutes[2]	59.96 ± 7.41	51.91 ± 6.32	6.417	< 0.001
Incision length, cm[1]	5.36 ± 1.26	4.78 ± 0.99	2.890	0.004
White blood cell count, × 10^9/L	8.54 ± 1.03	8.35 ± 1.31	0.800	0.425
Neutrophil count, %	59.75 ± 10.30	56.40 ± 9.72	1.783	0.077
CRP, mg/L	18.31 ± 3.14	19.41 ± 4.03	1.502	0.135
Diabetes	10	32	0.003	0.960
Hypertension	8	27	0.011	0.915

[1]$P < 0.05$, χ^2-test.
[2]$P < 0.05$, *t*-test.
CRP: C-reactive protein.

Table 2 Non-conditional logistic regression analysis of risk factors of postoperative incision infection in patients

Factor	B	SE	Exp (B)	Wald	Sig
Pathological type	2.243	0.842	9.419 (1.809-49.051)	7.097	0.008
Operation method	1.859	0.851	6.418 (1.210-34.037)	4.770	0.029
Surgery time	0.190	0.042	1.209 (1.114-1.312)	20.805	< 0.001
Incision length	0.470	0.232	1.601 (1.016-2.521)	4.117	0.042
Constant	-21.780	4.041	-	29.051	< 0.001

DISCUSSION

Anatomically, the appendix is long and narrow, making the lumen susceptible to fecal and bacterial retention. When the lymphatic tissue of the intestinal wall becomes infected, inflammatory reactions may occur, often resulting in pain. Surgical resection remains the most effective treatment for appendicitis as it alleviates abdominal pain, improves gastrointestinal function, and enhances the patient's quality of life. With recent advancements in medical technology, laparoscopic surgery has increasingly replaced traditional open surgery due to its benefits, including reduced incision size and pain. However, incision infection occasionally occurs after appendectomy and, in severe cases, a second surgery is required, which increases the physiological and psychological burden on patients.

Appendicitis with suppurative, gangrenous, and peripheral abscesses has a high risk of postoperative infection due to the fact that appendiceal infection is severe and may be accompanied by abdominal infection. The surgical incision associated with this surgery is in the right lower abdomen, where incomplete irrigation may have led to pelvic abscesses and abdominal infections. Patients who are older, malnourished, or have diabetes are prone to postoperative infections owing to low resistance. Additionally, factors such as improper surgical techniques, inadequate disinfection, insufficient incision protection, or suboptimal post-operative care further elevate the risk. The irregular, excessive, or inappropriate use of antibiotics also affects the prevention of infection, and ETX are cell wall components of gram-negative bacteria that are toxic to the host.

Table 3 Comparison of laboratory data between two groups, mean ± SD

Group	ETX (EU/mL)	TLR4 (ng/mL)
Infected group (n = 36)	0.36 ± 0.13	3.00 ± 0.83
Uninfected group (n = 117)	0.20 ± 0.06	2.17 ± 0.70
T	10.207	5.953
P value	< 0.001	< 0.001

ETX: Endotoxin; TLR4: Toll-like receptor 4.

Table 4 Predictive value of peripheral blood endotoxin, toll-like receptor 4 expression for postoperative incision infection

Index	Cutoff value	AUC	95%CI	*P* value	Sensitivity, %	Specificity, %
ETX	0.31	0.841	0.743-0.939	< 0.001	72.22	94.85
TLR4	2.94	0.769	0.679-0.858	< 0.001	52.84	88.00
Joint detection	-	0.922	0.873-0.972	< 0.001	86.11	85.54

AUC: Area under the curve; CI: Confidence interval; ETX: Endotoxin; TLR4: Toll-like receptor 4.

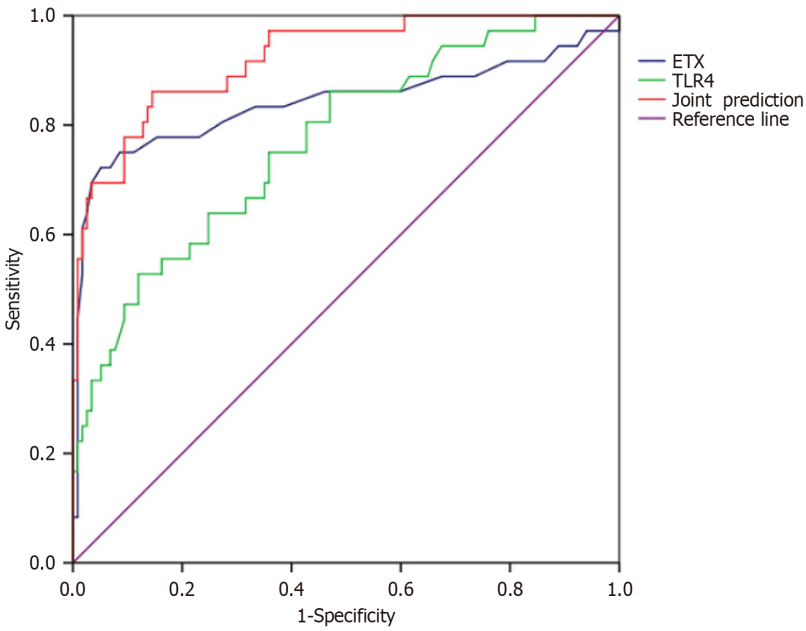


Figure 1 Receiver operating characteristic curve for predicting postoperative incision infection by peripheral blood endotoxin and toll-like receptor 4 expression. ETX: Endotoxin; TLR4: Toll-like receptor 4.

In acute appendicitis, bacterial infection causes bacterial death and the release of ETX, which can cause endotoxemia and increase the risk of postoperative infection. ETX cause symptoms, such as fever and microcirculation disturbances, and aggravate postoperative infection. TLR4 is an important immune receptor that recognizes pathogen-associated molecules, including ETX. In acute appendicitis, TLR4 expression is upregulated in response to infection; however, overactivation leads to excessive inflammation, aggravating tissue injury, and postoperative infections. After recognizing ETX, TLR4 triggers the release inflammatory factors such as interleukin-1 and tumor necrosis factor α, which are important in the inflammatory response, but may also aggravate postoperative infection. ETX and TLR4 interact with each other in postoperative infection of acute appendicitis and influence the development of infection together. Among the 153 patients with acute appendicitis enrolled in this study, 36 developed postoperative infections, accounting for 23.53%, similar to the incision infection rate of 22.62% reported in a study by Dong *et al*[11]. This confirmed that the risk of incision infection after appendectomy was high, and it is necessary to conduct a risk assessment early after surgery and provide corresponding intervention measures to reduce the risk of infection.

The results of this study demonstrated that the infected group had a higher proportion of patients with suppurative or gangrenous appendicitis compared to the uninfected group. This finding highlights the importance of implementing tailored infection prevention and treatment strategies for patients with acute appendicitis based on their pathological presentation. Patients with suppurative or gangrenous appendicitis exhibit a more severe inflammatory response, and the large amount of exudate can lead to cellular adhesion, which increases the risk of abdominal infection and further increases the risk of pathogenic bacteria infecting the incision site[12]. The higher proportion of patients in the infected group who underwent traditional open surgery and the relatively larger surgical incisions observed in this group suggest that open surgery carries a greater risk of incision infections in patients with acute appendicitis. The increased exposure of larger surgical incisions to the surrounding environment may elevate the risk of pathogen exposure. In contrast, laparoscopic surgery, with its smaller incisions, reduces the risk of pathogen exposure and subsequently lowers the incidence of postoperative incision infections[13]. Therefore, when selecting surgical procedures, the patient's pathological type and individual circumstances should be comprehensively considered. Operative time is another critical factor influencing postoperative incision infections, as prolonged surgical and incision exposure times increase the risk of pathogenic infection.

ETX is a complex of lipopolysaccharides and proteins that are primarily present in the cell walls of gram-negative bacteria. During the proliferation of gram-negative bacteria, the bacterial body undergoes lysis and ETX is released from the cell wall[14]. ETX has a strong stimulatory effect on neutrophils and macrophages in the body, which can lead to an increase in the levels of inflammatory factors, such as interleukin-6 and tumor necrosis factor, and participate in the inflammatory response[15]. TLR4 plays an important role in both acquired and innate immunity, as it can recognize the surface structure of various pathogens and participates in the body's inflammatory and immune responses[16]. Studies have shown that increased peripheral blood TLR4 expression may indicate a severe inflammatory response. After infection, pathogens can stimulate the synthesis and release of TLR4. Heat shock proteins released after cell necrosis can be recognized by TLR4, causing a cascade reaction that further activates downstream inflammatory cytokines[17]. Other studies have shown that TLR4 can activate signaling pathways, mediate the activation of nuclear transcription factor kappa B, and promote T cell proliferation and synthesis of inflammatory factors, thereby increasing the risk of infection in the body[18]. In the present study, the expression levels of ETX and TLR4 in the peripheral blood of patients in the infected group were significantly higher than those in the uninfected group. This is because infection can lead to the release of a large amount of ETX, which can increase the stress response of cells through contact with mononuclear cells, thereby leading to increased synthesis of TLR4. After recognizing inflammatory signals, TLR4 promotes the expression of downstream inflammatory factors, leading to increased severity[19,20]. ROC curve analysis showed that the expression levels of peripheral blood ETX and TLR4 had a certain predictive value for postoperative incision infection in patients, and the combined predictive value of the two was higher, indicating that the postoperative detection of ETX and TLR4 expression levels in peripheral blood has practical value for predicting postoperative incision infection in patients with acute appendicitis. This study has certain limitations. The small sample size may have introduced statistical bias, limiting the generalizability of the findings to clinical practice. Furthermore, this study did not analyze patients with different pathological types and surgical procedures separately, making it difficult to identify the factors influencing postoperative infections in patients with different pathological types or surgical procedures.

CONCLUSION

Pathological type, surgical method, surgical time, and incision length are significant factors influencing the occurrence of incision infections following surgery for acute appendicitis. Additionally, peripheral blood ETX and TLR4 expression levels exhibit predictive value for incision infections after appendectomy.

FOOTNOTES

Author contributions: Su W and Yang T contributed equally as co-first authors; Zhao XJ and Tang F contributed equally as co-corresponding authors; Su W performed the majority of the experiments and wrote the manuscript; Hu XJ and Huang D designed the study and corrected the manuscript; Yang T was involved in analytical tools; Song J and He JJ participated in the collection of human material; Zhang B and Zhao XJ served as scientific advisors and participated in the collection of human material; Tang F was the guarantor.

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ORIGINAL ARTICLE

Prospective Study

Prediction of perioperative complications in colorectal cancer *via* artificial intelligence analysis of heart rate variability

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Abstract

BACKGROUND

Heart rate variability (HRV) represents efferent vagus nerve activity, which is suggested to be related to fundamental mechanisms of tumorigenesis and to be a predictor of prognosis in various cancers. Therefore, this study hypothesized that HRV monitoring could predict perioperative complication (PC) in colorectal cancer (CRC) patients.

AIM

To investigate the prognostic value of HRV in hospitalized CRC patients.

METHODS

The observational studies included 87 patients who underwent CRC surgical procedures under enhanced recovery after surgery programs in a first-class hospital. The HRV parameters were compared between the PC group and the non PC (NPC) group from preoperative day 1 to postoperative day (Pod) 3. In addition, inflammatory biomarkers and nutritional indicators were also analyzed.

RESULTS
The complication rate was 14.9%. HRV was markedly abnormal after surgery, especially in the PC group. The frequency-domain parameters (including pNN50) and time-domain parameters [including high-frequency (HF)] of HRV were significantly different between the two groups postoperatively. The pNN50 was significantly greater at Pod1 in the PC group than that in the NPC group and returned to baseline at Pod2, suggesting that patients with complications exhibited autonomic nerve dysfunction in the early postoperative period. In the PC group, HFs were also enhanced from Pod1 and were significantly higher than in the NPC group; inflammatory biomarkers were significantly elevated at Pod2 and Pod3; the levels of nutritional indicators were significantly lower at Pod1 and Pod2; and the white blood cell count was slightly elevated at Pod3.

CONCLUSION
HRV is independently associated with postoperative complications in patients with CRC. Abnormal HRV could predicted an increased risk of postoperative complications in CRC patients. Continuous HRV could be used to monitor complications in patients with CRC during the perioperative period.

Key Words: Colorectal cancer; Heart rate variability; Complications; Perioperative period; Prediction

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Core Tip: In this study, heart rate variability (HRV) was compared among 87 patients who underwent colorectal cancer (CRC) resection. Abnormal HRV predicted a greater risk of postoperative complications in CRC patients. Continuous HRV could be used to monitor complications in patients with CRC during the perioperative period.

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INTRODUCTION

Colorectal cancer (CRC) is the second most prevalent cancer in the world, with case of 1.4 million and death of 693900 annually[1]. The only way to cure this disease is surgical excision. Nevertheless, postoperative complications not only directly exacerbate the patient's condition but also hinder or defer subsequent treatment. For example, they may cause the adjuvant chemotherapy to be postponed, thus influencing the long - term prognosis of oncology patients. In addition, postoperative complications occur in up to 50% of patients and are related to higher morbidity and mortality rates, greater expenditures on health care, and poorer quality of life[2-4]. Even though numerous preoperative measures, such as enhanced recovery after surgery (ERAS) programs, are conducted to minimize the risks of postoperative infections and complications, they can not eradicate them completely. Emerging evidence suggests that patients with postoperative complications have an abnormal autonomic nervous system (ANS)[5-9]. Heart rate variability (HRV) is reported as a measurement tool for quantifying the ANS and is modulated by the ANS.

HRV, defined as the variability between heartbeats, can be a noninvasive and standardized method to evaluate the prognosis of several diseases and ANS function[10,11]. HRV reflects complex coactions of the ANS, including vagus nerve, the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS)[12]. SNS activities advance the heart rate, whereas the PNS reduce it[10,13]. In addition to autonomic balance, HRV can also reflect the regulation of blood pressure (BP), breathing, the intestine, the heart, and angiotasis[14,15]. High HRV indices generally indicate efficient autonomic mechanisms, which are characteristic of a healthy individual. In contrast, low or decreasing HRV indices often signify a malfunction of the ANS and the possibility of health impairment[16]. HRV has two parameters: The time domain and the frequency domain. Recently, HRV has attracted extensive clinical interest, and it has also become an effective prognostic tool in intensive care medicine[17,18].

It has reported that patients with low HRV before surgery have a higher occurrence of postoperative complications [19]. However, few studies have evaluated perioperative complication (PC) and autonomic nerve dysfunction in patients with CRC *via* HRV. Our previous study revealed that, compared with current clinical indicators, perioperative HRV is more sensitive in detecting the stress and ANS dysfunction induced by radical gastrectomy in gastric cancer patients[20]. However, whether HRV could predict PC needs to be explored. Therefore, our study was designed primarily to explore fluctuations in the HRV through a noninvasive smart device that can continuously monitor HRV, further predict fluctuations in HRV, and analyze the role of HRV in monitoring PC in CRC patients.

MATERIALS AND METHODS

An observational study was conducted with patients with CRC from a first-class hospital. 87 patients who underwent CRC resection between December 2021 and December 2022 were enrolled consecutively. This study complies with the Declaration of Helsinki, written informed consent was given by all the subjects, and the study was approved by the local ethics committee. As reported in our previous study, patients were managed perioperatively *via* ERAS programs for colorectal resection in our department, including preoperative carbohydrate loading, multimode health education, no intestinal preparation for nonconstipated patients, laparoscopic surgery, early initiation of postoperative nutrition, shortened preoperative fasting time and oral carbohydrate administration, patient temperature maintenance, post-operative pain assessment and multimodal analgesia, early mobilization, and early oral feeding.

Inclusion criteria

Medical diagnostic criteria for CRC: Colonoscopy is the universally applied gold standard for CRC screening, *i.e.*, pre-operative colonoscopy biopsy pathologically confirms the diagnosis of CRC patients (developed with reference to the "Guidelines for Screening and Early Diagnosis and Treatment of CRC in China"). The inclusion criteria were as follows: (1) Age greater than 18 years old; (2) A diagnosed of CRC as clearly confirmed by preoperative colonoscopic biopsy pathology; (3) Underwent imaging examination to exclude distant metastasis and met the indications for surgery; (4) Not taking psychotropic drugs or cardiovascular disease drugs; (5) Clear consciousness, no communication barriers; (6) Body mass index (BMI) ranging from 18.5–26.9 before surgery; and (7) Minimally invasive laparoscopic or robotic-assisted laparoscopic surgery; and 8. Informed consent was obtained from the patients, and relevant consent forms were signed.

Exclusion criteria

The exclusion criteria were as follows: (1) Combined with breast or other endocrine or metabolic diseases; (2) The combination of coronary heart disease, atrial fibrillation, or heart, lung, liver, kidney, or other important organ failure; (3) Preoperative intestinal perforation, intestinal obstruction, intestinal necrosis, *etc.*, or emergency surgery; (4) Inability to give full informed consent due to intellectual or behavioral disabilities; and (5) Other pathologies that, in the judgment of the researcher, would reduce the likelihood of following through with enrollment or complicate the enrollment process, such as frequent changes in the work environment and other conditions that may lead to loss of visits.

Patients were managed perioperatively *via* ERAS programs for colorectal resection in our department, including preoperative and postoperative nutritional support, multimodal health education, no intestinal preparation for nonconstipated patients, shortened preoperative fasting time and oral carbohydrate administration, patient temperature maintenance, limited fluid resuscitation, postoperative pain assessment and multimodal analgesia, early mobilization, and early oral feeding.

Shedding criteria

Subjects who provided informed consent and were screened and qualified for enrollment but did not complete the course of treatment and observation period specified in the protocol for any reason or whose HRV data were discontinuous and had artifacts were regarded as dropout cases.

Data collection

A smart device (Transcendent THoughts On Health, THOTH, http://www.thoth-health.com/, Suzhou, China) was used for HRV monitoring. After the patients were admitted to the hospital, the researchers cleaned the skin of the precardiac area with wet gauze, attached the registered smart device to the skin in the shape of a T (Figure 1A), and uploaded the full-course heart rate to the monitoring system through the wireless transmission device. We analyzed the HRV in both the time and frequency domains and collected data from 24 hours before the operation to 3 days after the operation. After the data collection, Holter System software was used for statistical analysis (Figure 1C-F).

In addition to HRV, the collected variables included sex, age, BMI, underlying illnesses, surgical excision site, American Society of Anesthesiology (ASA) score, stage of cancer, *etc.* The study was approved by the Ethics Committee of the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine (Ethics Approval No. 2022NL-210-02) and complied with the principles of the Declaration of Helsinki.

HRV analysis

HRV measurement methods include Poincaré plots (Figure 1B), R–R interval histograms, time-domain analysis (power spectral density plot), and frequency-domain analysis (Figure 1C-F), among which time-domain and frequency-domain analysis methods are most widely used in clinical practice. The analyzed time-domain parameters included the standard deviation of N-N intervals (SDNN), the square root of the mean of the squared differences between adjacent normal RR intervals (RMSSD), and the percentage of NN50 count (number of consecutive RR intervals differing by > 50 ms in the entire recording) divided by the total number of all NN intervals (pNN50), which are based on the time difference. HRV frequencies can be summarized into three leading frequency bands: The very-low-frequency band, low-frequency (LF) band, and high-frequency band (HF). In addition, the ratio of LF power to HF power (LF/HF) reflects the balance between the SNS and PNS. All of these are frequency-domain parameters. In this study, one datum is obtained every day in the time-domain analysis, and each data point is the statistical result of all the obtained data on that day. In frequency-domain analysis, one data point is obtained in one day, which is a statistical result of monitored data on that day.

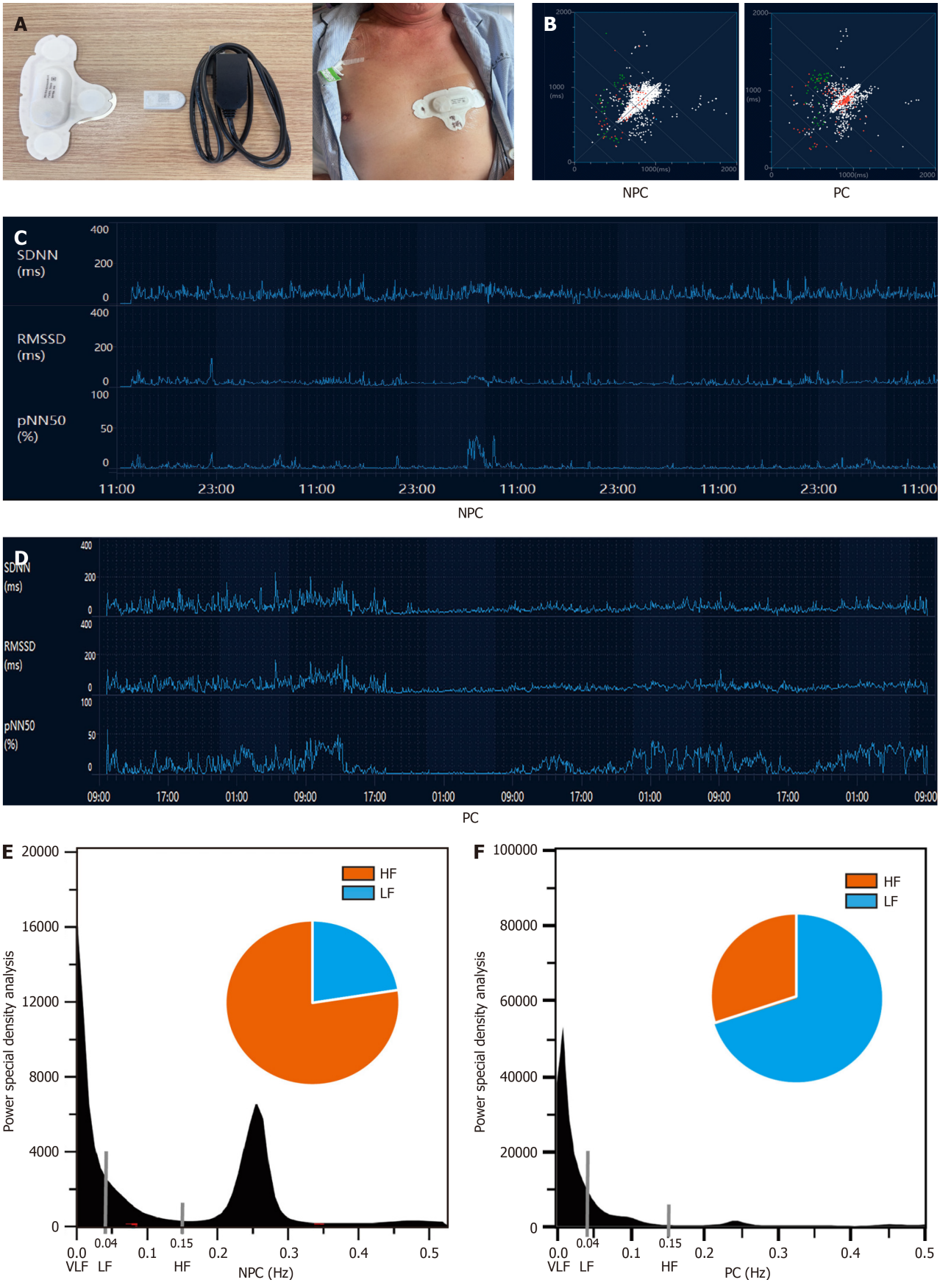


Figure 1 Heart rate variability in a normal and abnormal state. A: A smart monitoring device for the collection of heart rate variability data; B: Poincaré scatter diagram in a relaxed and stressed state; C and D: Trend chart of time-domain parameters indicating the difference 24 hours before the operation to 3 days after the operation; E and F: Power spectral density analysis of the frequency domain indicates the difference between the non-perioperative complication group and the perioperative complication group. NPC: Non-perioperative complication; PC: Perioperative complication; HF: High-frequency; LF: Low-frequency.

Statistical analysis

All the data were analyzed statistically using SPSS 19.0. The HRV data are shown as the mean ± SEM. All the data were tested for a normal distribution *via* the Shapiro-Wilk test. Nonnormally distributed data were described *via* the median (IQR) method. The longitudinal data were analyzed by paired-samples *t* test. The χ^2 test was used to compare categorical variables. Spearman's rank correlation coefficient was also used to evaluate the correlation between postoperative complications and HRV parameters or inflammatory indicators. Significance was defined as $P \leq 0.05$.

RESULTS

Patient characteristics

In this study, 87 patients who underwent CRC resection between December 2021 and December 2022 were enrolled consecutively; 13 patients were recorded as having PCs, and 74 patients had non-PC (NPCs). Table 1 outlines the patient characteristics. Comparisons of patients in the PC group vs. controls revealed no significant differences in age or sex distribution. Sex, BMI, ASA grade, surgical modality, underlying illness and disease stage were not significantly different between the two groups. The complications that occurred in 13 patients (14.9%), included anastomotic fistula, pulmonary complications, incisionostomy infection and urine retention.

Perioperative HRV analysis

All the perioperative HRV parameters, recovered to preoperative levels throughout the day at postoperative day 3 (Pod3) (Figure 1), although a certain degree of difference existed. The SDNN significantly differed between the two groups at Pod2 ($P < 0.01$) (Figure 2A). pNN50 was increased at Pod1, especially pNN50, which was significantly elevated at Pod1 in the PC group (Figure 2B). Interestingly, pNN50 was significantly increased at Pod1 and recovered to preoperative levels at Pod2. Compared with the NPC group, pNN50 was not significantly different at Pod2 and Pod3, indicating that pNN50 at Pod1 may be a predictor of complications. In addition, the RMSSD differed somewhat between the two groups, but the difference was not statistically significant (Figure 2C).

In our study, we found that LF parameters were not statistically different between the PC and NPC groups (Figure 2D). HF increased from Pod1 in the PC group, and LF/HF decreased to different degrees after surgery in the two groups (Figure 2E and F). Fascinatingly, the parameter of HFs in the PC group was markedly greater than that in the NPC group, and the HF indices increased in a time-dependent manner in the PC group (Figure 2E). Moreover, in the PC group, the LF/HF ratio was higher preoperatively; however, the LF/HF ratio decreased at Pod1 in the NPC group, and the ratio increased began to Pod2 (Figure 2F). These results indicated that HRV may be a predictor of complications, especially pNN50 and HF.

Perioperative inflammatory markers

Inflammatory markers were identified as sensitive markers for the early detection of complications (Figure 3 and Table 2). Compared with those before surgery, the inflammatory markers white blood cell (WBC) and C-reactive protein (CRP) increased significantly at different times after surgery. We found that the WBC count was significantly greater at Pod1 compared with Pre, indicating a markedly augmented inflammatory reaction at Pod1 (Figure 3A). However, there were no significant differences between the two groups except at Pod3. In addition, the CRP level increased after surgery in the PC group and significantly decreased at Pod2. Moreover, the level of CRP in the PC group was statistically greater at Pod2 and Pod3, comparing to that in the NPC group, which suggested that abnormally elevated CRP at Pod2 and Pod3 may be a predictor of complications (Figure 3B). Furthermore, albumin in the NPC group was higher than that in the PC group, especially at Pod1 and Pod2 ($P < 0.01$) (Figure 3C). These results indicated that the serum albumin level may be a risk factor for postoperative complications. However, Hb showed no statistical difference between the two groups (Figure 3D). All of these results suggested that abnormal inflammatory markers (CRP and albumin) were present in the PC group, indicating that abnormal inflammatory markers may be predictors of complications.

Furthermore, we analyzed the correlations between postoperative complications and HRV and inflammatory markers. We found that changes in HRV parameters (including pNN50 at Pod1 and HF at Pod3) and inflammatory biomarkers (including albumin levels at Pod1 and Pod2, CRP at Pod2 and Pod3, and WBC at Pod3) were correlated with postoperative complications ($P < 0.05$).

DISCUSSION

HRV represents vagus nerve activity, is inversely correlated with the underlying mechanisms of tumorigenesis, and has been shown to have predictive value in the prognosis of several cancers[5]. The relationship between HRV and complications in patients with CRC after surgery has not been reported. In previous studies, the HRV parameters were based on a 10-s ECG rather than long-range monitoring. In our study, we used continuous and longer-range monitoring to observe the HRV of patients with CRC perioperatively in real time. This study investigated whether continuous, long-range monitoring to observe HRV could predict postoperative complications in patients with CRC. Analysis of the HRV data of the patients with CRC enrolled in our study revealed that pNN50 and HF can be highly interrelated with PC, especially those measured at Pod1. However, the laboratory test indicator CRP significantly differed beginning on the Pod2. The results showed that the pNN50 and HF can be considered fairer indicators for predicting PC in patients with CRC.

Table 1 Patient characteristics, *n* (%)/mean ± SD

Parameters	Perioperative complications	Non-perioperative complications	*P* value
Gender			
Male	8 (14.5)	47 (85.5)	0.892
Female	5 (15.6)	27 (84.4)	
Age	61.85 ± 13.48	61.24 ± 10.70	0.857
BMI	22.54 ± 1.48	24.33 ± 3.20	0.052
Underlying illnesses			
Heart disease	1 (6.8)	5 (7.7)	0.444
Hypertension	2 (40.5)	30 (15.4)	
Diabetes	1 (7.7)	12 (16.2)	
Lung disease	0 (0)	1 (1.4)	
Nervous system disease	0 (0)	1 (1.4)	
Preoperative levels			
White blood cell (10^9/L)	6.35 ± 1.97	5.52 ± 1.75	0.130
Albumin (g/L)	39.35 ± 3.32	37.53 ± 4.62	0.329
Hb (g/L)	125.54 ± 19.54	122.55 ± 23.60	0.668
Surgical excision sites			
TME	5 (41.7)	27 (36.5)	0.56
Anterior resection	4 (33.3)	15 (20.3)	
Sigmoidectomy	0 (0)	6 (8.1)	
Left hemicolectomy	1 (8.3)	3 (4.1)	
Right hemicolectomy	2 (16.7)	23 (31.1)	
ASA Score			
1	3 (23.1)	18 (24.3)	0.936
2	7 (53.8)	36 (48.6)	
3	3 (23.1)	20 (27.0)	
Stage of cancer			
0	0	1 (1.5%)	0.719
I	2 (15.4)	14 (20.6)	
II	4 (30.8)	29 (42.6)	
III	7 (53.8)	23 (33.8)	
IV	0(0)	1 (1.5)	

BMI: Body mass index; TME: Total mesorectal excision; ASA: American Society of Anesthesiologists.

Surgical operations are thought to elicit complex physiological stress responses that involve the activation of endocrine, metabolic, immunological mediators and inflammatory which are the main causes of mortality[21]. Postoperative complications are risk factors for mortality in CRC patients and are often accompanied by severe stress responses[22]. Although we use the EARS program in the perioperative period to reduce stress[20], postoperative complications cannot be avoided. The usual methods for monitoring postoperative complications are dependent on laboratory test indicators, such as serum cortisol, CRP, WBC, and corresponding scales[23]. Recently, HRV has been used to detect autonomic function, inflammation status, and stress and has been used to prevent and monitor several diseases. Among these metrics, pNN50 is closely correlated with PNS activity, especially continuous pNN50. In our study, the time-domain parameter pNN50 revealed that the patients in the PC group had significantly greater vagus nerve activity at Pod1, suggesting more active parasympathetic nerve at Pod1 in the PC group. Both SNS and PNS activity contribute to the SDNN; the SDNN indicates total HRV, and a higher SDNN reflects greater health and physiological resilience[15,24]. Our study revealed that the peak SDNN was greater in the NPC group at Pod2, suggesting that a higher SDNN at Pod2

Table 2 Statistics of inflammation-related parameters between the two groups, mean ± SD

Parameters		Perioperative complications	Non-perioperative complications	*P* value
Pre	WBC (10^9/L)	6.35 ± 1.97	5.52 ± 1.75	0.130
	CRP (mg/L)	1.97 ± 2.25	5.84 ± 11.91	0.291
	Albumin (g/L)	39.35 ± 3.32	37.53 ± 4.62	0.329
	Hb (g/L)	125.54 ± 19.54	122.55 ± 23.60	0.668
Pod1	WBC (10^9/L)	10.87 ± 3.20	11.45 ± 3.61	0.589
	CRP (mg/L)	46.37 ± 80.47	25.48 ± 27.46	0.088
	Albumin (g/L)	32.09 ± 10.53	37.53 ± 4.62	0.003[b]
	Hb (g/L)	122.15 ± 14.77	115.17 ± 20.96	0.253
Pod2	WBC (10^9/L)	9.20 ± 2.75	8.38 ± 2.86	0.338
	CRP (mg/L)	73.66 ± 81.07	36.56 ± 41.77	0.017[b]
	Albumin (g/L)	33.97 ± 7.52	39.27 ± 4.23	0.001[c]
	Hb (g/L)	116.31 ± 16.04	113.78 ± 21.90	0.692
Pod3	WBC (10^9/L)	8.31 ± 3.04	6.76 ± 2.01	0.037[a]
	CRP (mg/L)	89.50 ± 86.65	16.35 ± 16.04	< 0.001[c]
	Albumin (g/L)	37.15 ± 6.31	38.97 ± 6.96	0.414
	Hb (g/L)	114.00 ± 16.20	119.87 ± 18.90	0.328

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$, the non-perioperative complication group group *vs* the perioperative complication group.
Pre: Preoperative day; Pod: Postoperative day; WBC: White blood cell; CRP: C-reactive protein; Hb: Hemoglobin.

predicts good short-term outcomes. HF is a well-known that HRV indices can imply the functional relevance of vagal and parasympathetic activity, especially during stress[24]. The HF in the PC group was statistically increased than that in the NPC group from Pod1, and it exhibited greater vagal activity indexed by the HF power of HRV in the PC group. These results indicated that higher vagal activity at Pod1 may predict an increased risk of complications.

In addition, the WBC count was significantly greater on Pod3 in the PC group than in the NPC group. CRP levels were significantly increased from the first day after surgery in the PC group (although some differences were not statistically significant), indicating that a higher CRP level can be used to predict the risk of postoperative complications. The Toon Health Study, which examined 1728 nonsmoking individuals aged 30-79 years from 2009 to 2012, expressed that HRV is highly relevant to an elevation in CRP[25]. However, our study revealed that abnormal pNN50 and HF test results appeared earlier than abnormal WBC and CRP test result did. These results are consistent with the theory of the ANS *via* an inflammatory reaction of the vagus nerve (the major nerve of the PNS), which is responsible for a quick reflexive response to inflammation[26]. This study showed that models using HRV as a parameter (including pNN50 and HF) were more sensitive than those using inflammatory markers for confirming postoperative complications. These results indicated that HRV was a more accurate indicator of postoperative complications in surgical patients than inflammatory markers. In addition, our team has routinely conducted the perioperative HRV monitoring in patients who have undergone gastrointestinal surgery. Our team implemented a perioperative ERAS strategy that resulted in a low postoperative complication rate. Therefore, a larger sample size study of PC is needed.

There are several limitations to the present study. First, our use of minimally invasive surgery (including Da Vinci robotic surgery and 3D laparoscopic), which minimizes the postoperative complication rate[27], resulted in a relatively small number of participants in the study. Second, we did not analyze the correlation of different complications with HRV due to the small number of samples. Third, factors such as patients' preoperative health status, medication regimens, and lifestyle elements could be potential confounding factors that impact HRV. Therefore, we took measures to reduce the influence of these potential confounding factors. As shown in the baseline data, there was no significant statistical difference between the two groups, however large-sample and long-term observational studies are needed. In the future, our research team will conduct relevant studies on the postoperative complications of CRC and gastric cancer to monitor and reduce the incidence of postoperative complications in patients and accelerate recovery after surgery.

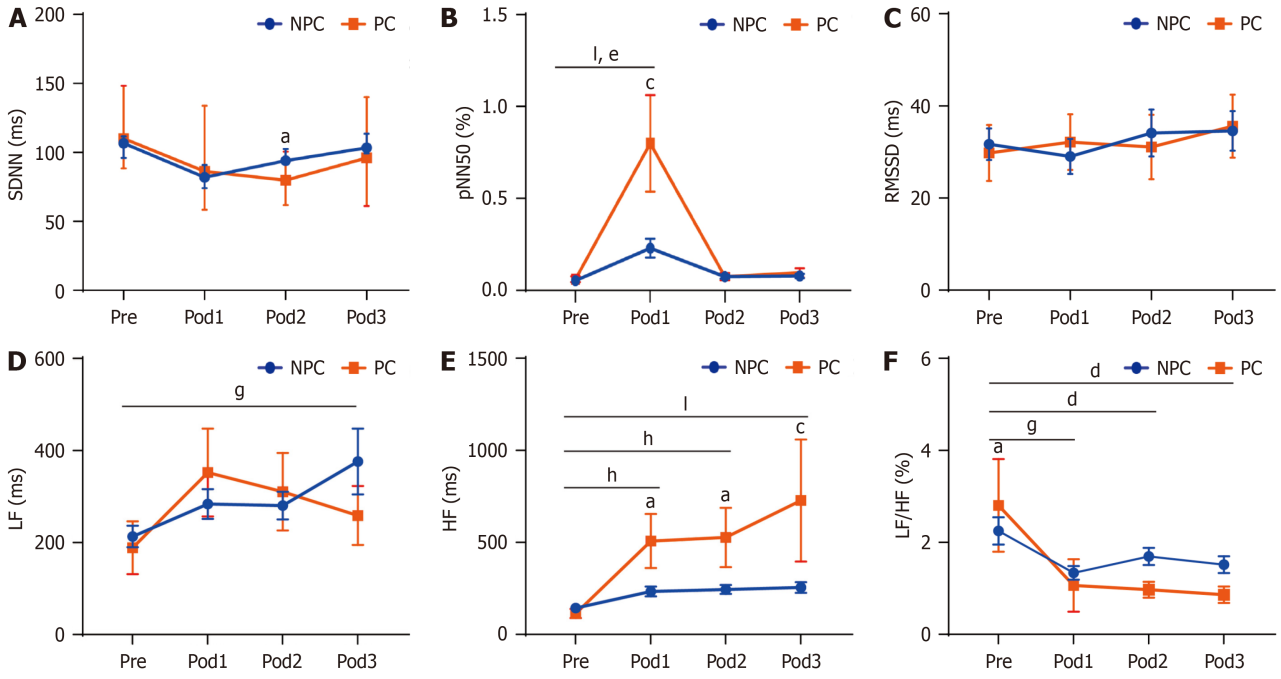


Figure 2 Fluctuation of time-domain and frequency-domain heart rate variability analysis parameters during the perioperative period in the perioperative complication group and non-perioperative complication group. A: The SDNN data throughout the day; B: The data of pNN50; C: The data of RMSSD; D: The data of LF; E: The data of HF; F: The data of LF/HF. [a]*P* < 0.05, [c]*P* < 0.001, the NPC group *vs* PC group; [g]*P* < 0.05, [h]*P* < 0.01, [l]*P* < 0.001, *vs* Pre in the non-perioperative complication group; [d]*P* < 0.05, [e]*P* < 0.01, *vs* Pre in the perioperative complication group. SDNN: Standard deviation of N-N intervals; RMSSD: Mean of the squared differences between adjacent normal RR intervals; LF: Low-frequency band; HF: High-frequency band; NPC: Non-perioperative complication; PC: Perioperative complication; Pre: Preoperative day; Pod: Post-operative day.

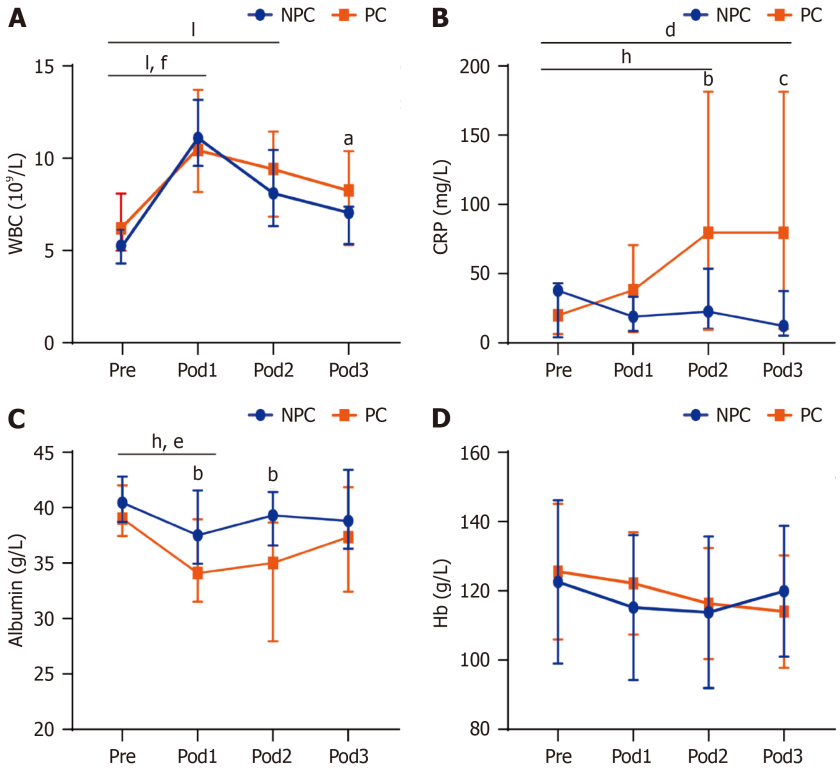


Figure 3 Inflammatory markers during the perioperative period in patients undergoing laparoscopic radical colorectal cancer resection. A: White blood cell of patients in the non-perioperative complication group (NPC) and perioperative complication (PC) group; B: C-reactive protein levels of patients in the NPC group and PC group; C: Albumin levels of patients in the NPC group and PC group; D: Hemoglobin levels of patients in the NPC group and PC group. [a]*P* < 0.05, [b]*P* < 0.01, [c]*P* < 0.001, with the NPC group *vs* the PC group; [h]*P* < 0.01, [l]*P* < 0.001, *vs* Pre in the NPC group; [d]*P* < 0.05, [e]*P* < 0.01, [f]*P* < 0.001, *vs* Pre in the PC group. WBC: White blood cell; CRP: C-reactive protein; Hb: Hemoglobin; Pod: Post-operative day.

CONCLUSION

In conclusion, our study indicated that continuous and long-term monitoring of the perioperative HRV of CRC patients may be valuable for predicting postoperative complications. Abnormal HRV occurs earlier than abnormal inflammatory markers. In addition, our study indicated that HRV could objectively reflect the change of autonomic nerve function perioperatively in patients with CRC and might be a worthy way for predicting PC and guiding clinical application in the context of precision medicine and artificial intelligence medicine. However, it would be meaningful to design larger, multicenter trials and investigate the predictive value of HRV in the context of other types of oncological surgeries.

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FOOTNOTES

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ORIGINAL ARTICLE

Prospective Study

Association between postoperative feeding patterns and gastrointestinal function reconstruction after congenital intestinal atresia in neonates

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Abstract

BACKGROUND

Congenital intestinal atresia (CIA) is a common intestinal malformation in the neonatal period, and surgery is currently the main treatment method. The choice of postoperative feeding is crucial for the recovery of gastrointestinal function in children.

AIM

To compare and analyze the effects of different postoperative feeding methods on gastrointestinal function reconstruction in newborns with CIA.

METHODS

Twenty-six children diagnosed with neonatal CIA, treated with minimally invasive surgery at Shijiazhuang Maternal and Child Health Hospital between January 2021 and May 2024, were selected for this single-center prospective randomized controlled study. They were divided into two groups using envelope randomization: Enteral nutrition (EN) group (n = 13) and parenteral nutrition (PN) group (n = 13). Baseline and clinical characteristics were collected, and recovery time of bowel sounds and time to first defecation were used as evaluation indices for gastrointestinal functional reconstruction. Differences between the groups were analyzed using t-test, χ^2 test, and Fisher's exact test. Spearman's correlation tests and linear regression models were employed to analyze factors influencing time to first defecation.

RESULTS

The time to bowel sound recovery (51.54 *vs* 65.85, P = 0.013) and first defecation

(58.15 *vs* 76.62, $P < 0.001$) was shorter in the EN group compared to the PN group. Clinical improvements in the EN group, including discharge weight ($P = 0.044$), hospital stay ($P = 0.027$), white blood cell count ($P = 0.023$), albumin content ($P = 0.013$), and direct bilirubin content ($P = 0.018$), were also better than those in the PN group. No substantial differences in postoperative complications were found between the groups. Correlation analysis indicated that abdominal infection and operation time may relate to time to first defecation. Linear regression analysis demonstrated a considerable association between EN feeding and shorter time to first defecation. Abdominal infection and an operation time > 2 hours may be risk factors for prolonged time to first defecation.

CONCLUSION

EN substantially promotes the recovery of gastrointestinal function after CIA in neonates and can improve clinical outcomes in children. Future research should explore optimal EN practices to enhance clinical application and child health.

Key Words: Congenital intestinal atresia; Enteral nutrition; Gastrointestinal function reconstruction; Neonatal postoperative feeding; Surgical prognosis

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Core Tip: This study demonstrated that enteral nutrition (EN) significantly accelerates gastrointestinal function recovery in neonates with congenital intestinal atresia after surgery compared to parenteral nutrition. EN reduces bowel sound recovery time and time to first defecation, while improving nutritional status and clinical outcomes. These findings highlight the importance of prioritizing EN in postoperative feeding strategies for neonatal congenital intestinal atresia to enhance recovery and overall prognosis.

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INTRODUCTION

Congenital intestinal atresia (CIA) is one of the most common intestinal malformations observed in the neonatal period, affecting approximately 1 in 5000 to 1 in 10000 live births[1]. Although the incidence of CIA is relatively low, it is a severe condition that often leads to substantial feeding difficulties and intestinal obstruction symptoms after birth. This condition markedly affects the growth and development of newborns, their quality of life, and can even pose life-threatening risks[2]. The pathogenesis of CIA is not fully understood; however, it is believed to be associated with small intestinal insufficiency during embryonic development, vascular accident, inflammatory infections, and genetic variations [3,4]. Surgery is currently the preferred treatment for CIA, because it can restore intestinal patency by removing the atretic segment of the intestine[5]. With advancements in medical technology, particularly the increased use of minimally invasive surgical techniques, the outcomes of surgical treatment for CIA in newborns have markedly improved, leading to enhanced postoperative survival rates[6]. Postoperative recovery in these children is influenced not only by the quality of the intestinal surgery but also by the reconstruction of intestinal function. Studies have indicated that faster recovery of intestinal function post-surgery correlates with a lower risk of surgery-related complications[7]. Therefore, the reconstruction of intestinal function serves as a key indicator for evaluating the efficacy of surgical treatment for CIA in children.

The choice of postoperative feeding mode has long been a key research focus in neonatal surgery. Currently, enteral nutrition (EN) and parenteral nutrition (PN) are two common nutritional support methods for newborns after surgery. EN is digested and absorbed *via* the gastrointestinal tract, stimulating the normal secretion of gastric acid, digestive fluids, and other digestive secretions; facilitate gallbladder contraction and gastrointestinal peristalsis; and contribute to the restoration of intestinal function[8]. However, EN may lead to feeding intolerance, insufficient nutrient intake, and other issues in children whose gastrointestinal function does not recover in the early postoperative period. In contrast, PN can bypass the damaged intestine, provide essential nutritional support, reduce intestinal burden, and facilitate intestinal rest and recovery[9]. However, long-term PN may lead to intestinal mucosal atrophy, intestinal flora imbalance, cholestasis, and other complications, which can adversely affect the recovery of intestinal function[10]. Therefore, selecting an appropriate feeding method to promote the reconstruction of gastrointestinal function after neonatal congenital atresia has become a focus of clinicians' attention.

Some studies have investigated the clinical effects of EN and PN after CIA in newborns; however, these studies have not investigated the relationship between EN and gastrointestinal functional reconstruction[11]. For children with CIA following surgery, the reconstitution of gastrointestinal function is critical for long-term prognosis and quality of life. Identifying the factors influencing intestinal function recovery in children after CIA surgery is essential for formulating

timely, targeted intervention strategies to promote postoperative recovery and improve prognosis. This study employed a prospective randomized controlled design to investigate the association between different feeding patterns and neonatal gastrointestinal functional reconstruction after CIA surgery. The findings of this study provide a theoretical basis for selecting postoperative feeding methods for newborns with CIA and will help optimize clinical treatment. Additionally, this study is anticipated to provide useful references for the postoperative feeding management of other types of congenital digestive tract malformations.

MATERIALS AND METHODS

Patient population

A total of 26 pediatric patients with CIA treated at Shijiazhuang Maternal and Child Health Hospital were included in this study, with a case collection period from January 2021 to May 2024. All patients met the following inclusion criteria: (1) Neonates diagnosed with CIA based on a comprehensive clinical evaluation; (2) Patients eligible for surgical intervention for CIA; and (3) Patients with complete clinical data. The exclusion criteria were as follows: (1) Patients with other severe congenital malformations or genetic disorders; (2) Patients with severe malnutrition or complications before surgery; (3) Patients with severe impairment or necrosis of intestinal function before surgery; and (4) Patients who abandoned treatment for various reasons. This study was approved by the Shijiazhuang Maternal and Child Health Hospital Ethics Committee, and all guardians of the children voluntarily provided informed consent.

Study design

A single-center prospective randomized controlled design was employed to investigate the effects of postoperative feeding patterns on gastrointestinal function reconstruction after CIA. All children were randomly assigned to either the EN group or the PN group immediately after surgery, with 13 patients in each group. The grouping was conducted using envelope randomization to ensure both randomness and blinding during the allocation process. After surgery, once it was confirmed that the patients met the inclusion criteria, a third party not involved in the follow-up treatment or evaluation assigned them to groups according to the instructions in the envelope, ensuring the fairness of the grouping results.

Data collection

Basic characteristics of the patients were collected, including age, sex, birth weight, location and type of CIA, duration of surgery, presence of abdominal infection, gestational duration, and length of bowel resection. Post-intervention characteristics of the patients were collected, including discharge weight, length of stay, complications, white blood cell (WBC) count, C-reactive protein, hemoglobin, albumin (ALB), and direct bilirubin (DB). After surgery, the abdomen was auscultated every 2 hours, and the time of the first recovery of bowel sounds was recorded, with clear, continuous bowel sounds lasting at least 3 minutes serving as the recovery standard. The time of the first excretion of fetal stool or formed stool after the surgery was recorded. Bowel sound recovery time and time to first defecation were used as indices to evaluate postoperative gastrointestinal function reconstruction.

Feeding pattern

In the EN group, once the vital signs of the children stabilized postoperatively, an appropriate amount of enteral nutrient solution was administered through a nasogastric or fistula tube as soon as feasible. In the early phase, infant formula or hydrolyzed protein formula, which is easily digestible and absorbable, was utilized as the EN solution. A small number of meals were provided, with the initial volume of each feeding kept moderate to avoid excessive intestinal burden. Generally, feeding started at 5-10 mL each time, gradually increasing to 20-30 mL or more, depending on the tolerance of the child. Feedings typically occurred 8-12 times per day to ensure the child received sufficient nutritional support. Simultaneously, the child's swallowing function and oral motor capacity were regularly evaluated in preparation for subsequent oral feeding. In the PN group, central or peripheral intravenous parenteral nutritional support was provided after surgery, including glucose, amino acids, fat milk, electrolytes, vitamins, and trace elements. The infusion volume and rate were adjusted based on the weight and nutritional requirements of the children, with a gradual transition to EN after the restoration of gastrointestinal function.

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. Continuous variables were described as mean ± SD and analyzed using independent sample *t*-tests. Categorical variables were described in terms of frequency and percentage, and comparisons between groups were conducted using the χ^2 test or Fisher's exact test. Spearman's correlation tests were employed to analyze the association between the time of the first bowel movement after surgery and other variables. In addition, with the time to first defecation as the dependent variable, a linear regression model was used to analyze factors influencing postoperative gastrointestinal function recovery. All statistical tests were two-tailed, and statistical significance was set at $P < 0.05$.

RESULTS

Basic characteristics of the two groups

A total of 26 neonatal patients with CIA were included in this study. The mean age of the PN group was 21.85 ± 14.15 hours, while the mean age of the EN group was 25.08 ± 16.12 hours, with no statistically significant difference between the two groups (P = 0.592) (Table 1). In addition, there were no substantial differences between the two groups in terms of sex, gestational duration, birth weight, length of intestinal resection, location and type of CIA, surgical duration, or the presence of abdominal infection (Table 1).

Differences between the two groups after intervention

The mean discharge weight of patients in the PN group was 3.09 kg, which was significantly higher than that of 3.56 kg in the EN group (P = 0.044) (Table 2). The mean length of hospital stay was significantly longer in the PN group than in the EN group (48.23 *vs* 35.62, P = 0.027) (Table 2). Regarding serum markers, there were significant differences in WBC (8.96 *vs* 7.98, P = 0.023), ALB (31.67 *vs* 34.29, P = 0.013), and DB (19.47 *vs* 12.31, P = 0.018) levels between the PN and EN groups (Table 2). No significant differences were observed in C-reactive protein (1.07 *vs* 1.15, P = 0.390) or hemoglobin (106.00 *vs* 111.92, P = 0.401) levels between the two groups (Table 2).

Postoperative complications in the two groups

Postoperative complications occurred in six patients (46.15%) in the PN group and three patients (23.08%) in the EN group, with no significant difference (P = 0.411) (Table 3). In the PN group, there were three cases of abdominal distension, two cases of emesis, and one case of incision infection after the intervention. In the EN group, there was one case of abdominal distension, two cases of emesis, and no cases of incision infection. No significant differences were found in the subgroup analysis of complications between the two groups (P > 0.05) (Table 3).

Gastrointestinal function reconstruction effect in the two groups

The recovery time of bowel sounds in the PN group was 65.85 ± 13.10 hours, while in the EN group it was 51.54 ± 13.91 hours (Table 4). The recovery time for bowel sounds was significantly shorter in the EN group than in the PN group (P = 0.013) (Table 4). The time to first defecation was 76.62 ± 12.04 hours in the PN group and 58.15 ± 12.95 hours in the EN group, indicating that the defecation recovery speed in the EN group was significantly faster than that in the PN group (P < 0.001) (Table 4). In summary, EN substantially promoted gastrointestinal function reconstruction after CIA surgery.

Correlation and regression analysis

Spearman's correlation analysis demonstrated a significant association between prolonged time to first defecation and the presence of abdominal infection (P = 0.004) (Figure 1). There was also a significant association between an operation time > 2 hours and delayed first defecation (P = 0.024) (Figure 1). The time to first defecation was used as the index of intestinal function recovery for linear regression analysis. The results indicated that EN feeding was associated with improved postoperative gastrointestinal function recovery (P < 0.001) (Figure 2). In addition, an operation time > 2 hours and the presence of abdominal infection limited the effectiveness of intestinal function recovery after CIA surgery (P < 0.001) (Figure 2).

DISCUSSION

CIA can lead to neonatal intestinal obstruction, which poses a serious threat to the lives of affected children[12]. Surgery is the only viable option for treating CIA in neonates, and the choice of postoperative feeding mode is of great significance for the recovery of gastrointestinal function and the long-term prognosis of these patients[13]. Although intravenous hyperalimentation is sufficient to correct malnutrition in the short term, long-term use may lead to multiple complications, such as hepatic steatosis, cholestasis, and intestinal flora imbalance[14]. EN can directly provide nutritional support to the intestine and promote the recovery and reconstruction of intestinal function, which is crucial for postoperative recovery[15]. Recently, increasing attention has been paid to the application of EN following CIA surgery. In this study, we compared the effects of EN and PN on the postoperative recovery of newborns with CIA using a single-center prospective randomized controlled design to provide a scientific reference for clinical practice. The results of this study are similar to those of previous studies, indicating that EN has a positive effect on intestinal function reconstruction after CIA surgery[7]. In addition, there are other findings of this study that will be elaborated upon in the following discussion.

One of the core findings was that, compared to PN, EN markedly reduced the time to bowel sound recovery and the time to first bowel movement in children with congenital atresia after surgery. These results directly support the beneficial role of EN in promoting postoperative recovery of gastrointestinal function. The recovery of bowel sounds and the occurrence of the first defecation are important indicators of restored gastrointestinal function[16]. Their early manifestation indicates recovery of intestinal motility and enhancement of intestinal barrier function. By directly stimulating the intestinal mucosa, EN promotes the secretion of intestinal hormones such as motilin and cholecystokinin, which are crucial for regulating intestinal movement and facilitating digestion and absorption[16]. In addition, EN helps maintain the balance of intestinal flora, reduces the reproduction of harmful bacteria, and promotes the recovery of intestinal function[17].

Table 1 Difference analysis of basic characteristics between two groups, *n* (%)

Variables	Total (*n* = 26)	PN group (*n* = 13)	EN group (*n* = 13)	Statistic	*P* value
Age (hour), mean ± SD	23.46 ± 14.95	21.85 ± 14.15	25.08 ± 16.12	*t* = -0.54	0.592
Sex				-	1.000
Female	14 (53.85)	7 (53.85)	7 (53.85)		
Male	12 (46.15)	6 (46.15)	6 (46.15)		
Gestation days (day), mean ± SD	256.00 ± 14.93	253.54 ± 14.76	258.46 ± 15.28	*t* = -0.84	0.412
Birth weight (kg), mean ± SD	2.87 ± 0.58	2.84 ± 0.58	2.91 ± 0.61	*t* = -0.31	0.761
Intestinal resection length (cm), mean ± SD	23.14 ± 7.58	23.90 ± 7.62	22.37 ± 7.76	*t* = 0.51	0.615
CIA location				-	1.000
Ileum	13 (50.00)	7 (53.85)	6 (46.15)		
Duodenum	9 (34.62)	4 (30.77)	5 (38.46)		
Colon	4 (15.38)	2 (15.38)	2 (15.38)		
CIA type				-	1.000
I and II type	11 (42.31)	6 (46.15)	5 (38.46)		
III and IV type	15 (57.69)	7 (53.85)	8 (61.54)		
Surgical duration				-	0.434
< 2 hours	13 (50.00)	5 (38.46)	8 (61.54)		
≥ 2 hours	13 (50.00)	8 (61.54)	5 (38.46)		
Abdominal infection				-	1.000
No	17 (65.38)	8 (61.54)	9 (69.23)		
Yes	9 (34.62)	5 (38.46)	4 (30.77)		

PN: Parenteral nutrition; EN: Enteral nutrition; CIA: Congenital intestinal atresia.

Table 2 The characteristics of the two groups after treatment

Variables	Total (*n* = 26)	PN group (*n* = 13)	EN group (*n* = 13)	Statistic	*P* value
Discharge weight (kg), mean ± SD	3.33 ± 0.60	3.09 ± 0.56	3.56 ± 0.57	*t* = -2.13	0.044[a]
Hospital stays (day), mean ± SD	41.92 ± 14.88	48.23 ± 15.01	35.62 ± 12.24	*t* = 2.35	0.027[a]
WBC (10^9/L), mean ± SD	8.47 ± 1.13	8.96 ± 1.04	7.98 ± 1.02	*t* = 2.43	0.023[a]
CRP (μg/mL), mean ± SD	1.11 ± 0.22	1.07 ± 0.21	1.15 ± 0.23	*t* = -0.88	0.390
HGB (g/L), mean ± SD	108.96 ± 17.57	106.00 ± 14.81	111.92 ± 20.12	*t* = -0.85	0.401
ALB (IU/L), mean ± SD	32.98 ± 2.78	31.67 ± 3.12	34.29 ± 1.63	*t* = -2.69	0.013[a]
DB (μmol/L), mean ± SD	15.89 ± 7.95	19.47 ± 8.14	12.31 ± 6.14	*t* = 2.53	0.018[a]

[a]*P* < 0.05.

PN: Parenteral nutrition; EN: Enteral nutrition; WBC: White blood cell; CRP: C-reactive protein; HGB: Hemoglobin; ALB: Albumin; DB: Direct bilirubin.

This study also found that EN positively affects clinical outcomes. Patients who received EN were discharged with higher body weight, had a shorter hospital stay, and exhibited lower WBC counts and DB levels, along with higher ALB levels. The comprehensive improvement in these indices reflects the advantages of EN in enhancing the overall nutritional status of children, reducing the inflammatory response, and promoting the recovery of liver function. The increase in discharge weight directly reflects improved nutritional status, while the shorter hospital stay indicates more effective use of medical resources and a reduced burden on families. A decrease in WBC count may indicate a reduction in the postoperative systemic inflammatory response, which is a positive indicator for recovery[18]. As one of the main proteins in the plasma, the increase in ALB content reflects improvements in nutritional status and intestinal function in the EN group[19]. DB is closely associated with liver metabolism and excretion. A decrease in DB typically indicates

Table 3 Analysis of postoperative complications in two groups, *n* (%)

Type	PN group (*n* = 13)	EN group (*n* = 13)	*P* value
Abdominal distension	3 (23.08)	1 (7.69)	0.593
Emesis	2 (15.38)	2 (15.38)	1.000
Incision infection	1 (7.69)	0 (0.00)	1.000
Total	6 (46.15)	3 (23.08)	0.411

PN: Parenteral nutrition; EN: Enteral nutrition.

Table 4 Effect of postoperative gastrointestinal function reconstruction in two groups

Variables	Total (*n* = 26)	PN group (*n* = 13)	EN group (*n* = 13)	Statistic	*P* value
Time of bowel sound recovery (hour), mean ± SD	58.69 ± 15.11	65.85 ± 13.10	51.54 ± 13.91	$t = 2.70$	0.013[a]
Time of first defecation (hour), mean ± SD	67.38 ± 15.45	76.62 ± 12.04	58.15 ± 12.95	$t = 3.77$	< 0.001[a]

[a]$P < 0.05$.
PN: Parenteral nutrition; EN: Enteral nutrition.

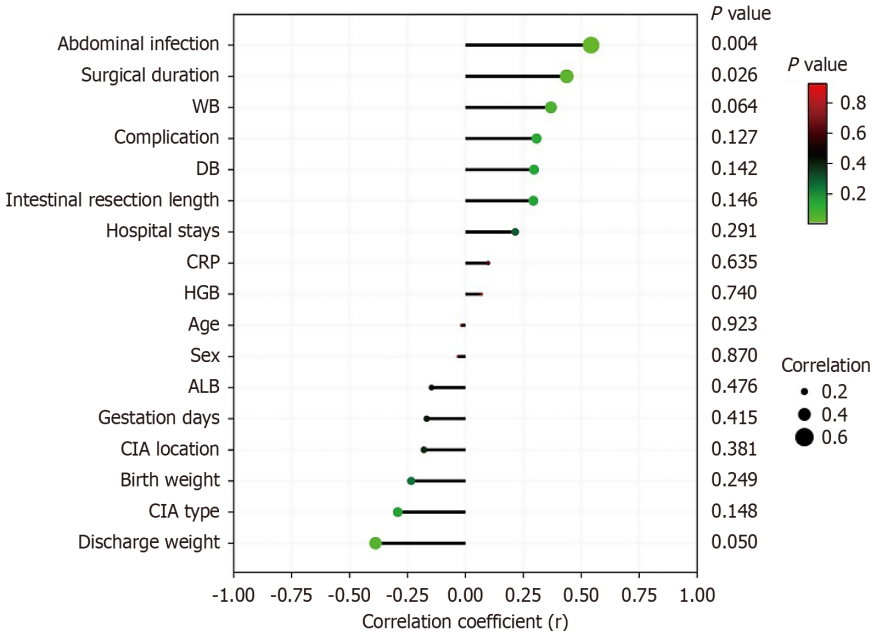


Figure 1 Lollipop plot for correlation analysis between first defecation time and other variables. WB: White blood cell; DB: Direct bilirubin; CRP: C-reactive protein; HGB: Hemoglobin; CIA: Congenital intestinal atresia.

improved liver function or unobstructed bile excretion, both of which are positive signs of liver function recovery[20]. The study also identified that abdominal infection and surgery duration greater than 2 hours as independent risk factors for prolonged recovery of bowel function in patients. As a common complication of CIA, abdominal infection can exacerbate the intestinal inflammatory response and destroy the intestinal mucosal barrier, thereby increasing surgical risks and prolonging the recovery of intestinal function[21]. Prolonged surgery duration may augment surgical trauma, affect blood circulation, and disrupt nerve regulation of the intestine, subsequently delaying recovery of intestinal function. Therefore, in clinical practice, considerable attention should be devoted to the prevention and treatment of abdominal infections, and efforts should be made to minimize surgical duration to mitigate adverse impacts on intestinal function.

In addition, the results of correlation analyses also showed that EN was significantly associated with shorter time to first bowel movement. The clinical significance of this finding lies in the fact that EN may promote the secretion of intestinal hormones (*e.g.*, gastric motility and cholecystokinin) through direct stimulation of the intestinal mucosa, thereby regulating intestinal motility and promoting digestion and absorption[22]. In addition, abdominal infections were significantly associated with prolonged time to first bowel movement. Abdominal infections may exacerbate the intestinal

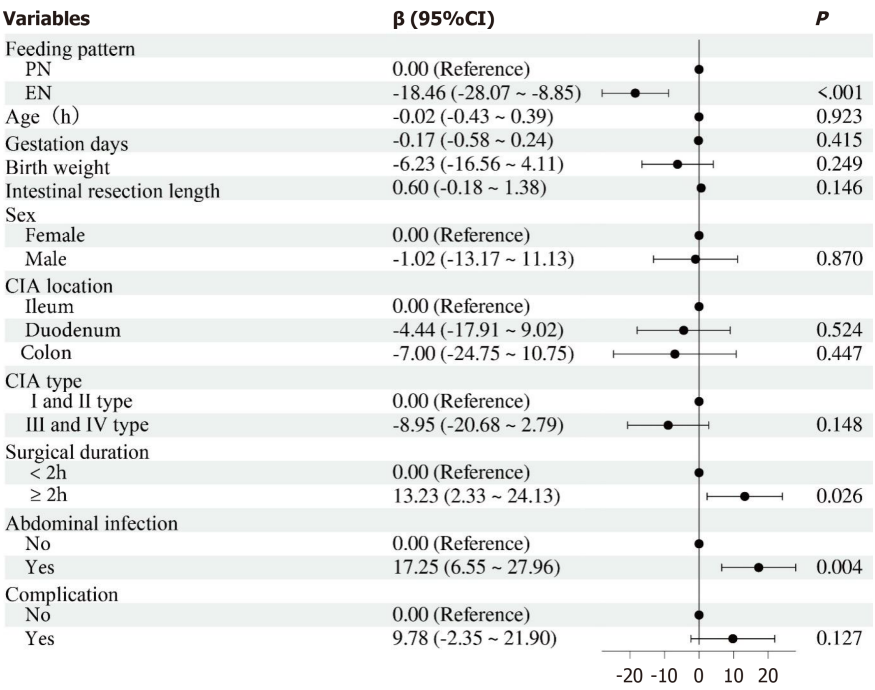


Figure 2 Linear regression analysis of factors affecting the first bowel movement time after congenital intestinal atresia surgery. PN: Parenteral nutrition; EN: Enteral nutrition; CIA: Congenital intestinal atresia; CI: Confidence interval.

inflammatory response and disrupt the intestinal mucosal barrier, thereby increasing the risk of surgery and prolonging the recovery of bowel function[23]. This finding highlights the importance of prevention and treatment of abdominal infections in clinical practice, as well as minimising trauma and controlling the duration of surgery to mitigate adverse effects on bowel function. Surgical times longer than 2 hours were associated with delayed recovery of bowel function. This may be due to the fact that longer surgical time may increase surgical trauma, affect blood circulation, and interfere with neuromodulation of the bowel, thus delaying the recovery of bowel function. This finding suggests that we should strive to optimise the surgical process and reduce unnecessary surgical time in our clinical practice to promote rapid recovery of bowel function in children after surgery.

Based on the findings of this study, we propose the following strategies for the clinical application of EN: First, EN should be initiated as soon as possible in children with CIA after surgery to fully utilize its promoting effect on gastrointestinal function recovery. Second, during EN implementation, the intestinal tolerance of children should be closely monitored, and the type, concentration, and infusion rate of the nutrient solution should be adjusted promptly to avoid the occurrence of excessive intestinal burden or insufficient nutrition. Finally, for children with abdominal infections or prolonged surgery durations, more proactive intervention measures should be taken, such as enhancing anti-infection treatment and optimizing the surgical plan, to shorten the recovery time of intestinal function and improve clinical outcomes.

Nevertheless, this study has some limitations. First, being a single-center study with a relatively small sample size may have introduced selection bias. Secondly, the follow-up time of this study is limited, and only the short-term effects of feeding methods on patients can be observed. Longer follow-up is needed to further evaluate the long-term benefits of both feeding regimens. Finally, the choice of feeding mode may be influenced by a variety of factors, such as financial burdens and consumption of medical resources, which are crucial considerations in clinical decision-making. This study indicates that EN has substantial advantages in promoting gastrointestinal function recovery after CIA surgery in newborns and can improve clinical outcomes in pediatric patients. Future research should focus on exploring the best practices for EN to better serve clinical practice and the health of pediatric patients.

CONCLUSION

Through prospective randomized controlled trials, this study revealed that EN was substantially superior in facilitating the restoration of gastrointestinal function in newborns after CIA surgery. Specifically, the recovery time of bowel sounds and the first defecation in the EN group was markedly shorter than in the PN group, thereby directly substantiating that EN can effectively stimulate intestinal motility and expedite recovery of intestinal function. Secondly, EN positively influences the nutritional status of children, mitigates systemic inflammatory responses, and promotes liver metabolic functions. Additionally, intraperitoneal infection and surgery duration exceeding 2 hours were identified as independent risk factors for prolonged recovery of bowel function in patients. In conclusion, the results of this study support prioritizing EN as a feeding modality after neonatal CIA to promote the rapid recovery of gastrointestinal function and enhance clinical outcomes. Future studies can further refine the implementation plan of EN and explore its application in

diverse clinical scenarios to offer more precise and effective nutritional support strategies in clinical practice.

FOOTNOTES

Author contributions: Zhao YZ designed the research; Kang HL performed the research, contributed to the new reagents or analytic tools, analyzed data, and wrote the paper.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Nursing care for patients with liver cirrhosis undergoing surgery for esophageal variceal bleeding in an integrated healthcare system

Wen-Xiu Su, Yun-Fei Li, Yi-Jun Zhu, Di-Wen Li

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Abstract

BACKGROUND

Globally, Liver cirrhosis is the 14th leading cause of death and poses a significant threat to human health.

AIM

To investigate the effects of a multidisciplinary collaboration model on postoperative recovery and psychological stress in patients with liver cirrhosis undergoing esophageal variceal bleeding (EVB) surgery within an integrated healthcare system.

METHODS

Between January 2022 and March 2024, a total of 180 patients with cirrhosis and EVB were admitted and randomly assigned to either a control group (standard care) or an observation group (standard care plus the multidisciplinary collaboration model), with 90 patients in each group. Postoperative recovery indicators (time to symptom improvement, time to start eating, time to bowel sound recovery, time to first flatus, and hospital stay), psychological stress responses [self-rating anxiety scale (SAS); self-rating depression scale (SDS)], subjective well-being, and incidence of complications were compared between the two groups.

RESULTS

Compared to the control group, the observation group showed earlier symptom improvement, earlier return to eating, bowel sound recovery, first flatus, and a shorter hospital stay. Pre-intervention SAS and SDS scores were not significantly different between the groups, but post-intervention scores were significantly lower in the observation group. Similarly, there was no significant difference in the subjective well-being scores before the intervention between the two groups. After the intervention, both groups showed improved scores, with the observa-

tion group scoring significantly higher than the control group.

CONCLUSION
The observation group also had a lower incidence of complications. Therefore, for patients with liver cirrhosis undergoing EVB surgery, a multidisciplinary collaboration model within an integrated healthcare system can promote early postoperative recovery, reduces psychological stress, improves subjective well-being, and reduces complications and rebleeding.

Key Words: Liver cirrhosis; Esophageal and gastric variceal bleeding; Integrated healthcare system; Multidisciplinary collaboration; Postoperative recovery; Psychological stress

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Core Tip: Effective nursing interventions play a crucial role for patients with cirrhosis who undergo esophageal variceal bleeding surgery. These interventions can significantly promote faster postoperative recovery and help reduce psychological stress, ultimately enhancing the overall well-being and quality of life of these patients.

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INTRODUCTION

Liver cirrhosis is a chronic and progressive disease characterized by symptoms such as fatigue, reduced appetite, and diarrhea, with high incidence and mortality rates. Globally, it is the 14th leading cause of death and poses a significant threat to human health[1]. Esophageal variceal bleeding (EVB) is a severe complication of cirrhosis that is indicative of decompensation and high mortality rates. It is estimated that 12%-85% of patients with cirrhosis have esophageal varices, with 41%-80% at risk of gastrointestinal bleeding because of rupture[2,3]. Timely surgical treatment of cirrhosis with EVB is crucial for hemostasis, blood volume restoration, portal pressure reduction, and the prevention of complications and rebleeding[4]. However, the severity of cirrhosis complicated by EVB, accompanied by significant blood loss and increased patient anxiety and fear, can lead to substantial psychological stress, which may affect the stability of the varices and hinder postoperative recovery[5]. Therefore, nursing interventions for patients undergoing surgical treatment for EVB are crucial. The multidisciplinary collaboration model, a leading approach in international medical practice, involves experts from various fields developing personalized intervention plans, thereby improving the quality of care [6]. The integrated healthcare system, a novel medical service model, integrates regional medical resources to build a collaborative service network, facilitates resource sharing and coordinated services, and enhances medical care efficiency. However, the impact of a multidisciplinary collaboration model within an integrated healthcare system on postoperative recovery and psychological stress in patients with cirrhosis undergoing EVB surgery has not yet been reported. In this study, we analyzed 180 patients with liver cirrhosis who underwent EVB surgery at our hospital between January 2022 and March 2024. Therefore, this study examined the effects of a multidisciplinary collaborative model within an integrated healthcare system on postoperative recovery and psychological stress in these patients.

MATERIALS AND METHODS

General data

Diagnostic criteria: Liver cirrhosis complicated by EVB was diagnosed based on endoscopic examination following expert consensus guidelines.

Inclusion criteria: Patients with a confirmed history of liver cirrhosis; presenting with symptoms, such as hematemesis, melena, and reduced hemoglobin levels; met surgical indications and scheduled for surgical treatment; had normal cognitive and communicative abilities; and provided informed consent from the patient or family.

Exclusion criteria: Patients with severe hepatic or renal failure, splenic abnormalities; malignancies; peptic ulcer disease; primary hematologic disorders; coagulation mechanism deficiencies; a history of endoscopic treatment for gastric varices; psychiatric illness or histories; and patients with severe anxiety or depression.

Selection of participants: A total of 180 patients with cirrhosis and EVB admitted to our hospital between January 2022 and March 2024 were selected using a random draw method and divided into control and observation groups, each

consisting of 90 patients. The control group comprised 52 males and 38 females, aged 52-76 years, with an average age of 64.00 ± 6.45 years, and a body mass index (BMI) ranging from 17 to 25 kg/m^2, with an average of 21.00 ± 3.12 kg/m^2. The Child-Pugh classifications were as follows: A, B, and C, with 20, 44, and 26 cases, respectively. The observation group included 55 males and 35 females, aged 51-76 years, with an average age of 63.50 ± 6.48 years, and a BMI ranging from 18 to 24 kg/m^2, with an average of 21.00 ± 2.80 kg/m^2. The Child-Pugh classifications were as follows: A, B, and C, with 22, 43, and 25 cases, respectively. The clinical data of the two groups were comparable ($P > 0.05$).

Methods

Control group: Standard care was provided, which included routine preoperative assessments, such as complete blood count, coagulation profiles, and electrocardiograms. The patients' conditions were closely monitored, and basic health education was provided to alleviate negative emotions through verbal counseling. They were informed of the perioperative precautions. The nursing staff strictly adhered to medical orders regarding medication administration and dietary guidance, and reported any abnormalities to the attending physician immediately. The patients were instructed to maintain a healthy lifestyle and undergo regular follow-up checks.

Observation group: In addition to standard care, a multidisciplinary collaboration model was implemented in the context of an integrated healthcare system.

Establishment of a multidisciplinary team: The integrated healthcare system consisted of one central hospital and five branch hospitals. The team comprised a chief physician from the Central Hospital's Gastroenterology Department with over 15 years of clinical experience, the director of intensive care units, a head nurse, branch hospital ward physicians, clinical pharmacists, deputy head nurses from the endoscopy department, a psychologist, a dietitian, and four nurses formed the nursing team.

Multidisciplinary training: Renowned experts in nursing for liver cirrhosis and EVB surgery, as well as in multidisciplinary collaboration models, were invited to share their knowledge through lectures. A multidisciplinary care manual was distributed to the team members, and a competency assessment was conducted before the commencement of the work. Only qualified individuals were included in the team.

Multidisciplinary consultations: Consultations were held to discuss patient treatment plans. Representatives from various departments expressed their opinions and reached a consensus through discussion.

Intervention methods of the multidisciplinary model: (1) Multidisciplinary ward rounds: Rounds were scheduled based on the availability of multidisciplinary personnel, with clear responsibilities assigned to each department. A WeChat group was established for enhanced communication and timely sharing of patient information. Major rounds were conducted every two days, involving the chief physician, ward physicians, and nurses, who meticulously reviewed all aspects of patient care, incorporated patient feedback, and made necessary adjustments; (2) Health education: During the treatment process, the responsible physician and nurse ensured a smooth handover, detailing the focus of care and potential safety hazards. Two designated nurses provided health education to the patients by distributing brochures and showing videos to inform them about surgery and postoperative precautions, increasing their understanding of the disease and surgery, and promptly answering their questions. The clinical pharmacist worked with the attending physician, developed a medication plan based on medical orders, physical examinations, and clinical data, and instructed the patients to strictly follow medical advice; (3) Psychological intervention: A psychologist assessed the patients' psychological states using the self-rating anxiety scale (SAS) and self-rating depression scale (SDS) and implemented appropriate psychological counseling measures based on the assessment results. Face-to-face communication has been used to alleviate psychological stress in patients with mild anxiety or depression through listening, empathy, and by guiding patients to express their thoughts. In moderate cases, relaxation techniques, such as deep breathing and muscle relaxation, were taught along with playing the preferred music, and medication was administered under the psychologist's guidance when necessary; (4) Diet guidance: The dietitian educated the patients and their families regarding the potential adverse effects of improper diets and developed individualized dietary plans based on the patient's condition, nutritional indicators, and dietary habits. Patients were advised to start consuming small amounts of warm water within 24 hours post-surgery, progressing to semi-liquid foods such as rice porridge, soft noodles, congee, and vegetable juice if no adverse reactions occurred. As their condition stabilized, a transition to soft foods was made, with strict avoidance of spiky, irritating, and hard foods. Dietary principles emphasized regular, small, frequent meals, and thorough chewing; and (5) Post-discharge follow-up: The multidisciplinary team arranged for a designated nurse to conduct post-discharge follow-ups with patients *via* telephone and WeChat for three weeks. These follow-ups tracked patients' conditions, addressed issues, and provided guidance for resolution.

Observational indicators

Postoperative recovery: The postoperative time to symptom improvement, first feeding, bowel sound recovery, first anal flatus, and total hospital stay were recorded for both groups.

Psychological stress response: SAS and SDS were used to assess psychological stress before and after the nursing intervention. Both scales consist of 20 items, scored from 1 to 4, with raw scores calculated by simple addition and then multiplied by 1.25 to obtain standard scores. Scores below 50 indicated no anxiety, whereas scores of 50 or above indicated anxiety. For the SDS, scores below 53 indicate no depression, and scores of 53 or above indicate depressive symptoms, with higher scores indicating greater severity[7].

Subjective well-being: Subjective well-being was assessed using a subjective well-being scale[8] before and after the nursing intervention. The scale consists of four dimensions (objective support, subjective support, self-assessment, and

subjective well-being index), with two, two, two, and three items, respectively, each scored from 1 to 4. The total score ranges from 9 to 36, with higher scores indicating greater subjective well-being.

Incidence of complications and rebleeding: Complications included upper gastrointestinal bleeding, electrolyte disorders, and hepatic encephalopathy.

Statistical analysis

Data from this study were processed using SPSS software (version 22.0). Categorical variables were presented as frequencies (n) and percentages (%), and analyzed for independence using the χ^2 test. Continuous variables were presented as mean ± SD, with independent samples t-test employed to assess mean differences between groups. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of postoperative recovery between groups

Compared to the control group, the observation group exhibited earlier symptom improvement, initiation of feeding, bowel sound recovery, and first anal flatus, with a significantly shorter hospital stay ($P < 0.05$; Table 1).

Comparison of psychological stress responses between groups

Before intervention, there was no significant difference in SAS and SDS scores between the groups ($P > 0.05$). After the intervention, the scores in both groups decreased, with the observation group showing significantly lower scores than the control group ($P < 0.05$). Patients in the observational group experienced a comparatively favorable psychological state, with reduced anxiety and depression levels (Table 2).

Comparison of subjective well-being between groups before intervention

There was no significant difference in the dimensions and total scores of subjective well-being between the two groups ($P > 0.05$). After the intervention, the scores in both groups increased, with the observation group scoring significantly higher than the control group ($P < 0.05$). These results highlight the effectiveness of nursing interventions (Table 3).

Comparison of complication rates between groups

The incidence of complications in the observation group was significantly lower than that in the control group ($P < 0.05$; Table 4).

DISCUSSION

EVB is a severe complication of liver cirrhosis, resulting from the progression of esophageal and gastric varices. It is characterized by rapid onset, fast disease progression, and high mortality rates. EVB is often a life-threatening condition that requires immediate medical attention[9]. Studies indicate that approximately 40%-95% of patients with liver cirrhosis develop esophageal varices, with approximately 15%-20% experiencing bleeding within 1-3 years of diagnosis[10]. Advances in endoscopic technology have led to an increasing number of patients opting for endoscopic treatment as the first choice. Common methods include endoscopic variceal ligation and injection sclerotherapy, which can directly occlude the varices to achieve hemostasis[11]. Clinical studies revealed that most patients with liver cirrhosis complicated by EVB surgery exhibit psychological stress responses, such as anxiety and depression, which are detrimental to surgical treatment and postoperative recovery[12]. Therefore, strengthening nursing interventions is crucial for patients undergoing surgical treatment for EVB. An integrated healthcare system maximizes the use of medical and health resources by fostering collaboration and resource sharing, improving the quality and efficiency of health services. Implementing a multidisciplinary collaboration model within this framework can enhance the efficiency of medical services and provide better medical services to patients.

Several studies have highlighted that enhanced recovery after surgery (ERAS) protocols, combined with comprehensive nursing care, ensure thorough preoperative education and psychological support, which are known to improve patient outcome. Consistent with these findings, the current study demonstrates that the application of a multidisciplinary collaborative model in EVB surgery facilitates earlier postoperative recovery. Patients in the observation group showed earlier recovery of postoperative symptoms and physical indicators ($P < 0.05$) compared to the control group, suggesting that the application of the multidisciplinary collaboration model under the integrated healthcare system can promote earlier postoperative recovery in patients. The integrated healthcare system, by efficiently pooling resources from various hospitals, helps improve the quality of medical management. Multidisciplinary collaborative nursing brings together experts from various departments to formulate comprehensive nursing plans tailored to patient needs. Multidisciplinary ward rounds enable a better understanding of patients' nursing needs and allow targeted adjustments to services based on their opinions and suggestions, thus effectively addressing existing problems. Health education increases patients' awareness of their condition and surgery, enhances self-care ability, and facilitates recovery. Dietary guidance ensures balanced nutrition, maintains body function, strengthens immunity, and promotes early postoperative

Table 1 Postoperative recovery in both groups

Groups	Cases	Time to symptom improvement (day)	Eating time (day)	Bowel sound recovery time (day)	Anal exhaust time (day)	Length of stay (day)
Control	90	2.85 ± 0.80	4.25 ± 0.70	2.30 ± 0.30	2.80 ± 0.40	9.50 ± 1.25
Observation	90	1.80 ± 0.35	2.70 ± 0.65	1.40 ± 0.25	1.45 ± 0.25	6.00 ± 1.05
t		11.408	15.393	21.864	27.151	20.340
P value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Table 2 Psychological stress responses in both groups

Groups	Cases	SAS (scores)		SDS (scores)	
		Before	After	Before	After
Control	90	56.65 ± 4.35	49.85 ± 3.20	59.55 ± 5.10	52.00 ± 3.60
Observation	90	57.00 ± 4.60	45.60 ± 3.35	60.20 ± 5.25	48.50 ± 2.90
t		0.524	8.703	0.842	7.183
P value		0.601	< 0.001	0.401	< 0.001

SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

Table 3 Subjective well-being in both groups

Groups	Cases	Objective support		Subjective support		Self-evaluation		Subjective happiness index		Total scores	
		Before	After	Before	After	Before	After	Before	After	Before	After
Control	90	3.10 ± 1.05	4.55 ± 1.20	3.25 ± 1.05	4.45 ± 1.30	3.95 ± 1.00	5.35 ± 1.00	7.20 ± 1.50	9.50 ± 1.05	17.50 ± 4.30	23.80 ± 5.00
Observation	90	3.25 ± 1.10	6.60 ± 1.25	3.30 ± 1.00	6.15 ± 1.20	3.98 ± 1.05	6.00 ± 1.10	7.00 ± 1.40	10.35 ± 1.10	16.95 ± 4.35	29.10 ± 4.50
t		0.936	11.224	0.327	9.116	0.196	4.148	0.925	5.303	0.853	7.475
P value		0.351	< 0.001	0.744	< 0.001	0.845	< 0.001	0.356	< 0.001	0.395	< 0.001

Table 4 Incidence of complications in both groups, *n* (%)

Groups	Cases	Upper gastrointestinal bleeding	Electrolyte disturbance	Hepatic encephalopathy	Total incidence
Control	90	9 (10.00)	6 (6.67)	5 (5.56)	20 (22.22)
Observation	90	2 (2.22)	1 (1.11)	1 (1.11)	4 (4.44)
χ^2					12.307
P value					< 0.001

recovery.

Psychological stress refers to an individual's physiological or psychological response to stressful events. Subjective well-being represents the overall emotional and cognitive evaluation that people make about their quality of life and is influenced by various factors. Patients with liver cirrhosis complicated with EVB often exhibit significant psychological stress responses and lower levels of subjective well-being[13,14]. Studies suggest that ERAS protocols are feasible and safe for patients with cirrhosis and can reduce postoperative complications and mortality rates. This study emphasized the improvement in psychological stress responses and subjective well-being, demonstrating the potential value of this model in enhancing postoperative recovery and psychological health in patients with cirrhosis. After the nursing interventions, the SAS and SDS scores in the observation group were lower than those in the control group, and the subjective well-being scores were significantly higher than those in the control group ($P < 0.05$), indicating that the multidisciplinary collaboration model under an integrated healthcare system could reduce psychological stress and improve the subjective well-being of patients. The analysis suggests that an integrated healthcare system can maximize the integration of resources, optimize services, and enhance service efficiency. Multidisciplinary collaboration can enhance diagnosis and treatment, facilitate resource sharing, and enable precise psychological services to patients. Health

education enabled patients to have a clear understanding of their condition, eliminating uncertainties, and improving psychological resilience. Psychological counseling tailored to scale assessment results effectively addresses psychological issues, fosters a sense of care and respect, and promotes improved subjective well-being.

Additionally, the incidence of complications in the observation group was significantly lower than that in the control group ($P < 0.05$), probably because of the implementation of a multidisciplinary collaborative model within an integrated healthcare system that provides multifaceted nursing services to patients, consistent with the findings of previous cohort studies[15]. Patients have a stronger awareness of self-care, better nursing outcomes, and faster recovery, ultimately reducing complication risk.

Therefore, future studies should include long-term follow-up to assess the effects of the multidisciplinary collaborative model on patient outcomes over time, including survival rates, recurrence rates, and quality of life metrics, with the aim of providing more optimal outcomes for the clinical treatment of cirrhosis with EVB.

CONCLUSION

In summary, a multidisciplinary collaboration model within an integrated healthcare system can enhance postoperative recovery, reduce psychological stress, improve subjective well-being, and reduce the incidence of complications in patients undergoing surgery for liver cirrhosis complicated by EVB. This approach is recommended for broader applications in clinical practice.

FOOTNOTES

Author contributions: Su WX designed the study; Su WX, Li YF, Zhu YJ, and Li DW analyzed the data; Su WX and Li YF were involved in the data collection and writing of this article; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Effectiveness of a multi-modal intervention protocol for preventing stress ulcers in critically ill older patients after gastrointestinal surgery

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Abstract

BACKGROUND

Stress ulcers are common complications in critically ill patients, with a higher incidence observed in older patients following gastrointestinal surgery. This study aimed to develop and evaluate the effectiveness of a multi-modal intervention protocol to prevent stress ulcers in this high-risk population.

AIM

To assess the impact of a multi-modal intervention on preventing stress ulcers in older intensive care unit (ICU) patients postoperatively.

METHODS

A randomized controlled trial involving critically ill patients (aged ≥ 65 years) admitted to the ICU after gastrointestinal surgery was conducted. Patients were randomly assigned to either the intervention group, which received a multi-modal stress ulcer prevention protocol, or the control group, which received standard care. The primary outcome measure was the incidence of stress ulcers. The secondary outcomes included ulcer healing time, complication rates, and length of hospital stay.

RESULTS

A total of 200 patients (100 in each group) were included in this study. The intervention group exhibited a significantly lower incidence of stress ulcers than the control group (15% *vs* 30%, $P < 0.01$). Additionally, the intervention group demonstrated shorter ulcer healing times (mean 5.2 *vs* 7.8 days, $P < 0.05$), lower

complication rates (10% *vs* 22%, $P < 0.05$), and reduced length of hospital stay (mean 12.3 *vs* 15.7 days, $P < 0.05$).

CONCLUSION
This multi-modal intervention protocol significantly reduced the incidence of stress ulcers and improved clinical outcomes in critically ill older patients after gastrointestinal surgery. This comprehensive approach may provide a valuable strategy for managing high-risk populations in intensive care settings.

Key Words: Stress ulcers; Older patients; Gastrointestinal surgery; Critical care; Multi-modal intervention

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Core Tip: This study evaluated a comprehensive multimodal intervention aimed at preventing stress ulcers in critically ill patients aged ≥ 65 years after undergoing gastrointestinal surgery. In a randomized controlled trial with 200 participants, the incidence of stress ulcers was significantly lower in those who participated in the intervention. These findings highlight the effectiveness of the multimodal approach and suggest that it may be a valuable strategy for improving clinical outcomes in vulnerable patient populations in intensive care settings.

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INTRODUCTION

Stress ulcers pose a major challenge in the management of critically ill patients, especially older individuals recovering from gastrointestinal surgery. These acute lesions in the gastric mucosa occur when severe physiological stress leads to reduced gastric blood flow and weakened mucosal defenses[1,2]. The incidence of stress ulcers in critically ill patients ranges from 0.6% to 6%, with higher rates observed in specific high-risk subgroups[3].

The older population, defined as individuals aged ≥ 65 years, is particularly vulnerable to stress ulcers owing to several factors. These include age-related changes in gastric mucosal integrity, increased comorbidities, polypharmacy, and reduced physiological reserves[4,5]. When combined with the stress associated with major gastrointestinal surgery and critical illness, these factors significantly increase the risk of developing stress ulcers.

Stress ulcers can be severe and potentially lead to gastrointestinal bleeding, perforation, and increased mortality. Moreover, these complications can prolong hospital stay, increase healthcare costs, and negatively impact patient outcomes[1]. As the global population continues to age and the number of older patients undergoing gastrointestinal surgery increases, effective strategies for preventing and managing stress ulcers in this high-risk group have become a clinical priority.

Current approaches to stress ulcer prophylaxis rely primarily on pharmacological interventions, particularly proton pump inhibitors (PPIs) or histamine-2 receptor antagonists[6]. Although these medications have shown efficacy in reducing the risk of stress ulcers, they have certain limitations. Concerns have been raised regarding potential adverse effects, including an increased risk of hospital-acquired pneumonia and Clostridium difficile infections[7]. Recent studies have also explored the role of other medications, such as pantoprazole, in stress ulcer prophylaxis[8].

Furthermore, the complex nature of stress ulcer pathogenesis in critically ill older patients suggests that a single intervention may be insufficient. Factors such as nutritional status, hemodynamic instability, mechanical ventilation, and coagulopathy contribute to the development of stress ulcers, indicating the need for a more comprehensive management strategy[9]. Mechanical ventilation is widely used among critically ill patients and is a known risk factor for the development of stress ulcers[10].

Despite recognizing these challenges, there is a paucity of research focusing on multi-modal approaches to stress ulcer prevention, particularly in older patients following gastrointestinal surgery[11]. Although some studies have explored individual interventions, a systematic, integrated protocol that simultaneously addresses multiple risk factors is yet to be thoroughly investigated in this patient population. Systematic reviews have highlighted the efficacy of interventions for preventing upper gastrointestinal bleeding in critically ill patients[12], underscoring the importance of effective prevention strategies in this population.

This study aimed to address this gap by developing and evaluating a multi-modal intervention protocol to prevent stress ulcers in critically ill older patients after gastrointestinal surgery. This protocol integrates various evidence-based strategies, including risk assessment, pharmacological prophylaxis, nutritional support, and stress management techniques, tailored to the unique needs of the older population.

MATERIALS AND METHODS

Study design and setting

This study was designed as a prospective randomized controlled trial conducted in the geriatric intensive care unit (ICU) of Jiangsu Province People's Hospital in China. The study protocol was approved by the hospital's Institutional Review Board, and written informed consent was obtained from all participants or their legal representatives.

Participants

Eligible participants were patients aged ≥ 65 years admitted to the geriatric ICU following gastrointestinal surgery between January 2022 and December 2023. The inclusion criteria were as follows: (1) Age ≥ 65 years; (2) Admission to ICU following elective or emergency gastrointestinal surgery; (3) Expected ICU stay of at least 48 hours; and (4) APACHE II score ≥ 10. The exclusion criteria were as follows: (1) Pre-existing gastric or duodenal ulcers; (2) History of gastrectomy or gastric bypass surgery; (3) Current use of anticoagulants or non-steroidal anti-inflammatory drugs (NSAIDs); (4) Severe hepatic dysfunction (Child-Pugh score C); (5) Pregnancy or breastfeeding; and (6) Participation in another interventional trial.

Sample size calculation

Based on previous studies, we estimated the incidence of stress ulcers in the control group to be approximately 30%. We hypothesized that our intervention would reduce this incidence by 15%. Using a two-sided alpha of 0.05, and power of 80%, we calculated that a sample size of 91 patients per group would be required. To account for potential dropouts, we recruited 100 patients per group for a total of 200 participants.

Randomization and blinding

Eligible patients were randomly assigned in a 1:1 ratio to either the intervention or control group using a computer-generated randomization sequence. The allocation was concealed using sequentially numbered opaque sealed envelopes. Due to the nature of the intervention, complete blinding of the patients and caregivers was not possible. However, the outcome assessors and data analysts were blinded to group allocation.

Intervention

Control group: Patients in the control group received standard care according to the hospital's existing postoperative ICU management protocols.

This included: (1) Routine monitoring of vital signs and laboratory parameters; (2) Standard stress ulcer prophylaxis with intravenous PPIs (esomeprazole 40 mg once daily); (3) Initiation of enteral nutrition as tolerated, typically within 24-48 hours post-surgery; (4) Standard pain management and sedation protocols; and (5) Regular assessments for complications.

Intervention group: Patients in the intervention group received a multi-modal stress ulcer prevention protocol in addition to standard care. The protocol consisted of the following steps: (1) Risk assessment: Daily assessments were performed using the modified Blatchford score to evaluate the risk of stress ulcer development. The modified Blatchford score evaluated the following parameters: Age (≥ 75 years: 2 points, 65-74 years: 1 point), mechanical ventilation (2 points), coagulopathy (INR > 1.5: 2 points), shock requiring vasopressors (2 points), acute kidney injury (1 point), and major surgery duration > 4 hours (1 point). Risk categorization was based on a total score of the following: Low risk (0-3 points), moderate risk (4-6 points), and high risk (≥ 7 points). Assessments were performed at admission and every 24 hours thereafter. Documentation of risk scores in electronic health records was performed using automated alerts for score changes; (2) Pharmacological prophylaxis: Tailored stress ulcer prophylaxis based on risk assessment; low-risk: No pharmacological prophylaxis. Moderate-risk: Intravenous ranitidine 50 mg every 8 hours. High-risk: Intravenous esomeprazole 40 mg twice daily; (3) Early Enteral Nutrition: Initiation of enteral nutrition within 24 hours of ICU admission unless contraindicated. The initial feeding rate was 20 mL/h, with an increase of 20 mL/h every 8 hours, if well tolerated. Target rate calculation based on 25-30 kcal/kg/day. Gastric residual volume monitoring every 4 hours: If < 250 mL: Continue current rate, if 250-500 mL: Reduce rate by 50% and reassess in 4 hours, if > 500 mL: Hold feeding for 4 hours, reassess, and restart at 50% of the previous rate; daily calculation of actual *vs* target caloric intake; initiation of supplemental parenteral nutrition if < 60% of caloric goals met by enteral route after 72 hours. The protocol includes specific guidance for handling feeding interruptions during procedures or tests; (4) Hemodynamic optimization: Targeted fluid resuscitation to maintain adequate tissue perfusion. Vasoactive agents were used as needed to maintain a mean arterial pressure of > 65 mmHg. Continuous monitoring of the central venous oxygen saturation ($ScvO_2$) and lactate levels; (5) Stress management: Implementation of a multicomponent delirium prevention program. Daily sedation interruption and assessment of extubation readiness: Early mobilization protocol tailored to the patient's condition. Use of music therapy and relaxation techniques; (6) Glycemic control: Maintenance of blood glucose levels between 140-180 mg/dL. Regular insulin levels were adjusted according to a standardized protocol; (7) Oral care: Implementation of a comprehensive oral hygiene protocol. The intubated patients were orally rinsed twice daily with chlorhexidine; (8) Positioning: Elevation of the head of the bed to 30-45 degrees, unless contraindicated. Positional changes were made every 2 hours to prevent pressure ulcers; (9) Medication review: Daily review and adjustment of medications to minimize gastric irritants. Avoidance of unnecessary antibiotics and NSAIDs; and (10) Education and communication: Daily multidisciplinary rounds to ensure protocol adherence. Regular education sessions for nursing staff on stress ulcer prevention. Clear communication with patients and families regarding prevention strategies.

Outcome measures

Primary outcome: Incidence of stress ulcers during ICU stay, diagnosed by upper gastrointestinal endoscopy or clinical evidence of upper gastrointestinal bleeding.

Secondary outcomes: (1) Time to healing of stress ulcers (for patients who developed ulcers); (2) Incidence of stress ulcer-related complications (*e.g.*, clinically significant bleeding, perforation); (3) Length of ICU stay; (4) Length of hospital stay; (5) 30-day mortality rate; (6) Incidence of ventilator-associated pneumonia; and (7) Incidence of Clostridium difficile infection.

Data collection

Baseline data, including demographic information, comorbidities, type of surgery, APACHE II score, and laboratory values, were collected at enrollment. During ICU stay, daily assessments were performed to monitor the development of stress ulcers and other outcomes. All patients underwent upper gastrointestinal endoscopy upon ICU discharge or earlier, if clinically indicated. Follow-up data were collected until hospital discharge or 30 days after enrollment, whichever occurred first.

Statistical analysis

All analyses were performed on an intention-to-treat basis. Continuous variables are expressed as mean ± SD or median with interquartile range, depending on the distribution of the data. Categorical variables are expressed as frequencies and percentages.

For the primary outcome, the incidence of stress ulcers was compared between the two groups using the χ^2 test. Risk ratios with 95% confidence intervals (CIs) were calculated. Time-to-event outcomes were analyzed using Kaplan-Meier curves and compared using the log-rank test.

For secondary outcomes, continuous variables were compared using student's *t*-test or Mann-Whitney *U* test, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test.

To adjust for potential confounding factors, multivariable logistic regression analysis was performed for the primary outcome, including pre-specified variables such as age, APACHE II score, type of surgery, and comorbidities.

All statistical tests were two-sided; a *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Patient characteristics

A total of 278 patients were assessed for eligibility between January 2022 and December 2023. Of these, 200 met the inclusion criteria and were randomized to either the intervention group (n = 100) or the control group (n = 100).

The baseline characteristics of the study participants are presented in Table 1. The two groups were well balanced regarding demographic characteristics, comorbidities, type of gastrointestinal surgery, and severity of illness as measured by the APACHE II score.

Primary outcome

The incidence of stress ulcers was significantly lower in the intervention group than in the control group (15% *vs* 30%, P = 0.009). The risk ratio for developing stress ulcers in the intervention group was 0.50 (95%CI: 0.29-0.85). The number needed to treat (NNT) to prevent one case of stress ulcer was 6.7 (95%CI: 4.0-20.0).

Secondary outcomes

Table 2 summarizes the secondary outcomes in both groups. Ulcer healing time was significantly shorter in the intervention group than in the control group (5.2 ± 2.1 days *vs* 7.8 ± 3.4 days, P = 0.003). The incidence of stress ulcer-related complications was also lower in the intervention group (3% *vs* 9%, P = 0.04). Patients in the intervention group had a shorter median length of ICU stay (5 days *vs* 7 days, P = 0.01) and a shorter mean length of hospital stay (12.3 ± 5.6 days *vs* 15.7 ± 7.2 days, P = 0.001) compared to the control group. While there was a trend towards lower 30-day mortality in the intervention group, this difference did not reach statistical significance (8% *vs* 13%, P = 0.25). Similarly, there was a trend towards a lower incidence of ventilator-associated pneumonia in the intervention group; however, this was not statistically significant (7% *vs* 15%, P = 0.07).

Subgroup analysis

A pre-planned subgroup analysis was performed to assess the effect of the intervention across different risk categories based on the modified Blatchford score. Table 3 presents the results of this study. The intervention appeared to be the most effective in the high-risk subgroup, with a significant reduction in the incidence of stress ulcers (30.4% *vs* 59.1%, P = 0.05). The effect was less pronounced but still notable in the moderate-risk group, whereas there was no significant difference in the low-risk group.

Multivariable analysis

After adjusting for potential confounding factors (age, APACHE II score, type of surgery, and presence of diabetes), the

Table 1 Baseline characteristics of study participants, *n* (%)

Characteristic	Intervention group (*n* = 100)	Control group (*n* = 100)	*P* value
Age, years (mean ± SD)	73.5 ± 6.2	74.1 ± 5.9	0.47
Male sex	58 (58)	55 (55)	0.67
BMI, kg/m² (mean ± SD)	24.3 ± 3.8	24.7 ± 4.1	0.46
APACHE II score (mean ± SD)	18.3 ± 5.7	17.9 ± 6.1	0.63
Type of surgery			
Gastric	28 (28)	30 (30)	0.75
Colorectal	45 (45)	42 (42)	0.67
Hepatobiliary	18 (18)	20 (20)	0.72
Pancreatic	9 (9)	8 (8)	0.80
Comorbidities			
Hypertension	62 (62)	59 (59)	0.66
Diabetes mellitus	35 (35)	38 (38)	0.66
Coronary artery disease	28 (28)	25 (25)	0.63
COPD	15 (15)	18 (18)	0.57
Chronic kidney disease	12 (12)	10 (10)	0.65
Mechanical ventilation	78 (78)	75 (75)	0.61
Vasopressor use	45 (45)	48 (48)	0.67

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease.

Table 2 Secondary outcomes, *n* (%)

Outcome	Intervention group (*n* = 100)	Control group (*n* = 100)	*P* value
Ulcer healing time, days (mean ± SD)[1]	5.2 ± 2.1	7.8 ± 3.4	0.003
Stress ulcer-related complications	3 (3)	9 (9)	0.04
Length of ICU stay, days [median (IQR)]	5 [3-8]	7 [4-11]	0.01
Length of hospital stay, days (mean ± SD)	12.3 ± 5.6	15.7 ± 7.2	0.001
30-day mortality	8 (8)	13 (13)	0.25
Ventilator-associated pneumonia	7 (7)	15 (15)	0.07
Clostridium difficile infection	2 (2)	5 (5)	0.25

[1]Among patients who developed stress ulcers. ICU: Intensive care unit.

Table 3 Incidence of stress ulcers by risk category, *n* (%)

Risk category	Intervention group	Control group	*P* value
Low risk	2/35 (5.7)	4/33 (12.1)	0.35
Moderate risk	6/42 (14.3)	13/45 (28.9)	0.09
High risk	7/23 (30.4)	13/22 (59.1)	0.05

intervention remained significantly associated with a lower risk of stress ulcer development (adjusted OR 0.42, 95%CI: 0.21-0.84, $P = 0.01$).

Protocol adherence

Overall adherence to the multi-modal intervention protocol was high, with a mean adherence rate of 89% across all components. The highest adherence was observed for pharmacological prophylaxis (98%) and early enteral nutrition (95%), whereas the lowest adherence was observed for stress management (78%).

DISCUSSION

This randomized controlled trial demonstrated that a multi-modal intervention protocol significantly reduced the incidence of stress ulcers in critically ill older patients following gastrointestinal surgery. The comprehensive approach, which integrated risk assessment, tailored pharmacological prophylaxis, early enteral nutrition, and various supportive measures, resulted in a 50% relative risk reduction in stress ulcer development compared with standard care.

The observed incidence of stress ulcers in our control group (30%) was consistent with previous reports of high-risk critically ill patients[1,3]. The reduction to 15% in the intervention group represented a clinically meaningful improvement, with the NNT being 6.7. This suggests that one case of stress ulcer can be prevented for every seven patients treated with the multi-modal protocol.

A key strength of our intervention was the use of a dynamic risk assessment tool, the modified Blatchford score, to guide pharmacological prophylaxis. This approach allows for more targeted use of acid-suppressive medications, potentially minimizing unnecessary exposure and associated risks. The specific operational process for risk assessment and intervention measures enhances the reproducibility of the study by addressing the reviewers' recommendations. When comparing our study to similar multi-modal intervention studies, our protocol was more comprehensive in simultaneously addressing multiple risk factors. For instance, while previous studies have focused primarily on individual pharmacological prophylaxis or nutritional support, our integrated approach combined these with stress management and hemodynamic optimization. This holistic strategy distinguishes our study and its unique contributions to the field.

Subgroup analysis revealed that the intervention was particularly effective in high-risk patients, supporting the value of risk stratification in stress ulcer prevention strategies. This finding aligns with previous research that emphasized the importance of tailored interventions based on patient risk profiles[11]. The assessment of organ dysfunction using scoring systems like the Sepsis-related Organ Failure Assessment score provides valuable prognostic information and can guide interventions in critically ill patients[13].

In our study, hemodynamic optimization was an essential component of the intervention protocol, aiming to maintain adequate tissue perfusion and prevent organ dysfunction. This aligns with the recommendations from the Surviving Sepsis Campaign guidelines, which emphasize the importance of maintaining mean arterial pressure and adequate organ perfusion in critically ill patients[14]. By adhering to these guidelines, we aimed to reduce the risk of organ failure, which is a contributing factor in stress ulcer development.

The significant reduction in ulcer healing time observed in the intervention group (5.2 *vs* 7.8 days) suggests that the multi-modal approach not only prevents ulcer formation but also promotes faster healing when ulcers occur. This finding may be attributable to the comprehensive nature of the intervention, which addressed the multiple factors involved in ulcer pathogenesis and healing, including tissue perfusion, nutritional status, and stress reduction.

The lower incidence of stress ulcer-related complications in the intervention group (3% *vs* 9%) is an important finding, as these complications can significantly affect patient outcomes and healthcare costs. By preventing severe bleeding and perforation, the multi-modal protocol may reduce morbidity and mortality rates in this high-risk population.

Advances in endoscopic diagnostic and therapeutic techniques have significantly improved the detection and management of gastrointestinal complications[15]. By integrating such advancements into patient care, alongside preventive strategies, further improvements in patient outcomes can be achieved. The observed reductions in ICU and hospital length of stay were particularly noteworthy. The median ICU stay was 2 days shorter in the intervention group, while the mean hospital stay was reduced by 3.4 days. These findings have significant implications for patient outcomes and healthcare resource utilization. Shorter ICU and hospital stays may lead to a reduced risk of hospital-acquired infections, improved quality of life for patients, and substantial cost savings for healthcare systems. However, our study did not demonstrate a statistically significant reduction in 30-day mortality, and there was a trend towards lower mortality in the intervention group (8% *vs* 13%, $P = 0.25$). The study may have been underpowered to detect differences in this outcome, and larger trials focusing specifically on mortality as the primary outcome are warranted.

The trend towards a lower incidence of ventilator-associated pneumonia in the intervention group, although not statistically significant, was an interesting finding. This may be related to components of the protocol, such as early mobilization, oral care, and potentially reduced use of high-dose acid suppression. Further research is required to explore the potential effects of stress ulcer prevention strategies on ICU-related complications.

The high adherence rate to the multi-modal protocol (89%) suggests that the intervention is feasible for implementation in real-world ICU settings. Lower adherence to the stress management component (78%) highlights an area for potential improvement, possibly through additional staff training or the development of more user-friendly tools to implement these techniques in critically ill patients. Addressing these adherence challenges is crucial for maximizing the effectiveness of the protocol and ensuring its consistent application in clinical settings. The comprehensive nature and detailed operational processes of our protocol enhance its applicability and reproducibility. Unlike studies that may focus on

single interventions or lack detailed implementation guidelines, our study provides a robust framework that can be adapted and applied to various medical environments, thereby clarifying its innovation and unique contributions.

Future research could focus on optimizing the multi-modal intervention protocol by refining the components with lower adherence and exploring the integration of additional preventive measures. Moreover, future studies should investigate the applicability of the protocol in different healthcare settings, including multicenter trials, to validate its effectiveness across diverse patient populations and clinical practices. In addition, a comprehensive cost-effectiveness analysis would provide valuable insights into the economic benefits of implementing such protocols on a larger scale.

Our study has several strengths, including its randomized controlled design, use of clinically relevant outcomes, and focus on a specific high-risk population of older patients after gastrointestinal surgery. The multi-modal nature of the intervention addresses the complex pathophysiology of stress ulcers and provides a holistic approach for their prevention and management.

However, this study had some limitations. First, its single-center design may limit the generalizability of our findings to other settings with different patient populations and care practices. Future multicenter trials are required to validate these results in diverse healthcare settings. Second, due to the nature of the intervention, complete blinding of the patients and caregivers was not possible, which may have introduced bias. However, the outcome assessors and data analysts were blinded to the group allocation to minimize potential bias. Third, although we observed significant improvements in several clinical outcomes, our study was not powered to detect differences in less frequent events, such as mortality. Larger studies with longer follow-up periods are necessary to fully elucidate the impact of this intervention on long-term outcomes. Fourth, we did not conduct a formal cost-effectiveness analysis. While the reduction in ICU and hospital length of stay suggests potential cost savings, a comprehensive economic evaluation would be valuable for informing healthcare policies and resource allocation decisions. Finally, our study focused on the prevention of stress ulcers and did not extensively investigate the potential adverse effects of the intervention, such as the long-term consequences of acid suppression or the risk of hospital-acquired pneumonia. Future studies should include more comprehensive assessments of the benefits and potential risks of intensive stress ulcer prevention strategies.

CONCLUSION

In conclusion, our study demonstrated that a multi-modal intervention protocol significantly reduced the incidence of stress ulcers and improved several clinical outcomes in critically ill older patients following gastrointestinal surgery. The emphasis of the protocol on individualized risk assessment, tailored pharmacological prophylaxis, early nutritional support, and comprehensive care measures provides a promising framework for stress ulcer prevention in this high-risk population.

FOOTNOTES

Author contributions: Xi HM and Chu MJ jointly the concept of this study and participated in data collection; Xi HM drafted the initial; Tian ML, Tian YL, and Liu H contributed to the formal analysis of this study; Wang Y guided the research, methodology, and visualization of the manuscript; Xi HM, Tian ML, Tian YL, Liu H, Wang Y, and Chu MJ participated in this study, validated it, and jointly reviewed and edited the manuscript. Xi HM and Chu MJ contributed equally to this work as co-first authors.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Modified single-port laparoscopic appendectomy using needle-type grasping forceps *vs* conventional three-port laparoscopic appendectomy for acute uncomplicated appendicitis

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Abstract

BACKGROUND

Single-port laparoscopic appendectomy is an advanced minimally invasive surgery that involves the use of upgraded instruments and equipment. We previously modified single-port laparoscopic appendectomy with needle-type grasping forceps (mSLAN) for patients with simple appendicitis, but the feasibility and safety of our modified procedure need further evaluation in a high-quality clinical study.

AIM

To compare the short-term clinical outcomes of mSLAN with those of conventional three-port laparoscopic appendectomy (CLA) for patients with acute uncomplicated appendicitis.

METHODS

This single-center, single-blind, prospective, randomized controlled trial included patients who underwent emergency laparoscopic appendectomy for acute uncomplicated appendicitis at our center between April 2024 and August 2024. Patients were randomly divided into the mSLAN group or the CLA group *via* computer-generated randomization. The primary endpoint was the 24-hour postoperative visual analog scale (VAS) score, and the secondary endpoints included the ope-

rative time, 24-hour postoperative inflammatory response biomarkers (including white blood cells, the neutrophil ratio, interleukin-6, and C-reactive protein), time to first postoperative exhaust, time to first out-of-bed activity, postoperative length of hospital stay, cost of hospitalization, and incidence of postoperative complications.

RESULTS

A total of 72 patients were enrolled and randomly divided into 2 groups: The mSLAN group (n = 36) and the CLA group (n = 36). The 24-hour VAS scores, 24-hour postoperative inflammatory response marker levels, first postoperative exhaust times, first out-of-bed activity times, postoperative lengths of hospital stay, operative times, or hospitalization costs did not significantly differ between the two groups. No postoperative complications, including incision infection or hernia, abdominal abscess or intestinal obstruction, were observed during the 1-month postoperative follow-up in either group.

CONCLUSION

Compared with the CLA protocol, the mSLAN protocol for acute uncomplicated appendicitis yielded comparable short-term clinical outcomes, with a similar operative time and better cosmetic outcomes, indicating its potential for clinical application and superiority for patients with high cosmetic requirements. Further research is needed to evaluate the long-term outcomes.

Key Words: Single-port laparoscopy; Minimally invasive surgery; Acute appendicitis; Appendectomy; Randomized controlled trial

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Core Tip: In this study, the short-term clinical outcomes of modified single-port laparoscopic appendectomy using needle-type grasping forceps (SLAN) were compared with those of conventional three-port laparoscopic appendectomy. Our results demonstrated the feasibility, safety, effectiveness, and clinical application potential of the modified SLAN protocol, which is an alternative minimally invasive surgical protocol for patients with acute uncomplicated appendicitis.

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INTRODUCTION

Acute appendicitis, a well-known cause of abdominal pain, affects millions of patients worldwide, with an annual incidence rate of 96.5-100/100000, which remains one of the most common pathologies resulting in hospital admission, with hospitalization cost in the United States alone at 3 billion dollar annually[1,2]. Many treatment strategies are available for acute appendicitis, such as anti-inflammatory drugs, surgical interventions, and endoscopic retrograde appendicitis therapy[2-8]. Despite ongoing debates, each protocol has specific indications, advantages and limitations.

As the primary protocol for surgical intervention, appendectomy has been widely performed, and with the rapid development of minimally invasive surgical techniques, laparoscopic appendectomy has gradually replaced traditional open surgery. However, the surgical trauma and stress associated with conventional three-port laparoscopic appendectomy (CLA) are somewhat severe for acute uncomplicated appendicitis with slight inflammation. Thus, at our center, we designed a novel technique-single-port laparoscopic appendectomy with needle-type grasping forceps (SLAN) to improve surgical outcomes. In previous studies, researchers compared CLA with SLAN and reported that SLAN produced satisfactory surgical and cosmetic outcomes[9].

Nevertheless, the size of the trocar (5 mm) used in SLAN limits its application in patients with a severely edematous appendix, the narrow operating space affects the fluency of the operation, the absence of long ham-o-lock clips and sterile gauze increases the potential risk of inflammatory complications, and the duration of the procedure extends its learning curve, further limiting its clinical application. Further modifications are needed to ensure stable maintenance of pneumoperitoneum pressure and easy sterile sample removal; thus, significant progress needs to be made prior to the broad adaptation of SLAN. To solve the above problems, a modified protocol was designed. Two trocars were directly inserted into the abdominal cavity instead of *via* the initial open pathway to stabilize the pneumoperitoneum pressure; moreover, two trocars with sizes of 5 mm and 10 mm were used to improve the space of the surgical channel and facilitate the use of long ham-o-lock clips and gauze and the removal of the thickened appendix. The surgical details were also further modified to alleviate challenges related to the parallel relationship in single-port laparoscopic surgery and consequently improve the fluency of the surgery and shorten the surgical time.

However, the modified protocol extends the umbilical incision to 1.5 cm, and whether the short-term clinical results and cosmetic results of this procedure are comparable to those of the conventional three-port surgical protocol is unclear; thus, high-level medical evidence is needed. Therefore, this prospective, randomized controlled trial was designed to introduce this novel single-port protocol and evaluate its safety and efficacy.

MATERIALS AND METHODS

Study design and patient selection

This work is a single-center, single-blind, prospective, randomized controlled trial. Patients with a preoperative diagnosis of acute uncomplicated appendicitis (acute simple and suppurative appendicitis) who were hospitalized between April 2024 and August 2024 at Chaoyang Central Hospital in Liaoning Province, China, were prospectively enrolled. The preoperative diagnosis was based on each patient's medical history, abdominal physical examination, preoperative laboratory tests, and abdominal ultrasound or computed tomography scans. The follow-up protocol was performed by two investigators (Yuan JQ and Song L). The home address and contact information of each patient were recorded in detail, and the office telephone number of the investigators was also disclosed to the patients. At discharge, the patients were advised to contact the investigators and visit the outpatient clinic in case of any physical complaints. Moreover, the patients were routinely followed up at an outpatient clinic *via* telephone interviews or *via* social networks 1 month after surgery to record postoperative complications, including incision infection, hernia, abdominal abscess or intestinal obstruction. Informed consent was obtained from all the included patients. The study protocol was approved by the Ethics Committee of Chaoyang Central Hospital, China Medical University (No. 2024-03) and was prospectively registered in the Chinese Clinical Trials Registry (No. ChiCTR2400081025). The reporting of this study conforms to the CONSORT 2010 statement[10].

Sample size calculation

In our previous retrospective analysis[8], the maximum 24-hour visual analog scale (VAS) pain score was 0.38 ± 0.79 for SLAN patients and 1.05 ± 10.86 for CLA patients (P = 0.0004). According to the sample size calculation, 34 patients were needed in each group to achieve 80% power to detect superiority using a one-sided, two-sample unequal-variance t test. The margin of superiority was -0.1. The actual difference between the means was assumed to be -0.67. The significance level (alpha) of the test was 0.025. The data were drawn from populations with standard deviations of 0.79 for group 1 and 0.86 for group 2. According to the sample size calculation and considering a 10% drop rate, 38 patients were needed for each group.

Randomization and blinding

Random numbers were generated using SAS version 9.4 (SAS Institute Inc., NC, Cary, United States) and sealed in individual envelopes. The envelopes were randomly opened by a designated researcher before surgery. Patients with odd numbers were included in the modified SLAN (mSLAN) group, and patients with even numbers were included in the CLA group. The umbilicus and left and right lower quadrants of all patients were covered with sterile gauze to conceal the actual surgical protocol.

Inclusion criteria: (1) Preoperative diagnosis of acute uncomplicated appendicitis (acute simple and suppurative appendicitis); (2) 2-70 years of age; and (3) Agreed to participate in this study and signed a written informed consent form.

Exclusion criteria: (1) Intraoperative or postoperative diagnosis of acute complicated appendicitis (acute gangrene and perforated appendicitis) or malignant tumors requiring further treatment; (2) Refusal to undergo surgery; (3) Underwent open surgery (including conversion to open surgery); (4) Severe cardio-cerebrovascular disease or other surgical contraindications; (5) Lost to follow-up; (6) Insufficient case data; and (7) Refusal to participate (including midway withdrawal).

Discharge criteria: (1) No fever, abdominal distension, severe pain or other complications that require clinical intervention; (2) The incision healed well; and (3) Eating normally without difficulties in flatulence or defecation.

Primary and secondary endpoints

The primary endpoint was the 24-hour postoperative VAS score[11], and the secondary endpoints were as follows: (1) Operative time, 24-hour postoperative inflammatory response biomarkers [including white blood cells (WBCs); neutrophil ratio (NEU%); C-reactive protein (CRP); and interleukin-6 (IL-6)]; (2) Time to first postoperative exhaust; (3) Time to first out-of-bed activity; (4) Postoperative length of hospital stay; (5) Hospitalization cost; and (6) Incidence of postoperative complications, including incision infection or hernia, abdominal abscess, or intestinal obstruction.

Surgical procedures

A surgeon (Chen Y) from our center with extensive experience in laparoscopic procedures performed all the surgeries. All participants were informed of the purpose, protocol, potential risks and benefits of the study and provided written informed consent before surgery. Under general anesthesia, the patient was placed in a supine position, and the carbon dioxide (CO_2) pneumoperitoneum pressure was set according to the patient's age (13 mmHg for adults and 8 mmHg for children). The laparoscopic display screen was placed on the right side of the patient. Laparoscopes were manufactured

by STORZ Corporation of Germany, disposable trocars and needle-type grasping forceps were manufactured by Hangzhou Kangji Medical Instrument Corporation of China, and disposable bags were manufactured by Hangzhou Weide Medical Technology Corporation of China. The appendix was sent for pathological examination after surgery.

mSLAN group

A mSLAN protocol was used. A 10 mm long umbilical incision was made, CO_2 pneumoperitoneum was established, and a 10 mm disposable trocar was inserted into the abdominal cavity. The patient was repositioned such that the head was angled 30° downward and the body was tilted 30° to the left. The surgeon stood to the lower left, and the assistant stood to the upper left. A 5 mm caliber 30° laparoscope (Karl Storz SE and Co. KG, Tuttlingen, Germany) was placed to explore the abdomen, ensuring assessment of the status of the abdominal infection, determination of adhesions, and visualization of the appendix. The incision was lengthened along the left of the umbilicus by 5 mm, and a 5 mm trocar was then inserted to place a 30° laparoscopic lens and to display surgical fields, while needle-type grasping forceps (Approval No. zsyjx 20140056; Hangzhou Kangji Medical Instrument Co., Ltd., Hangzhou, China) were inserted at the McBurney site. Next, the 10 mm trocar was moved forward to the right iliac fossa until it was observed in the surgical field (Figure 1).

A sterile gauze was inserted through the 10 mm trocar to prevent bleeding and exudation. An ultrasound scalpel was used to free the mesentery of the appendix. Longer Ham-o-lock absorbable clips were inserted to clip the root and distal end of the appendix, after which the appendix was resected. To ensure that no bleeding or secondary injury occurred, the sterile gauze was removed, and the appendix was removed and carefully placed in a disposable bag through the 10 mm trocar. The CO_2 pneumoperitoneum was resolved, and the skin around the umbilical incision was disinfected with iodophor and alcohol in sequence. The incision was sutured with 3-0 absorbable threads (Figure 2A). The detailed procedures and intraoperative imaging data were reported previously[12].

CLA group

The CLA protocol was performed in this group. First, a 12 mm long umbilical incision was made, and CO_2 pneumoperitoneum was established. A 12 mm disposable trocar was then inserted to serve as the main port for the operation and removal of the appendix. Next, the patient was repositioned so that the head was angled 30° downward and the body was slightly tilted 30° to the left. The surgeon stood to the upper left, and the assistant stood to the lower left. A 10 mm disposable trocar was then placed at the converse McBurney site for laparoscopic observation, a 5 mm trocar was inserted at the McBurney site for assisted operations (Figure 2B), and the remaining procedures, such as laparoscopic exploration and appendectomy, were similar to the mSLAN protocol previously described.

Statistical analysis

All clinical data were analyzed using statistical product and service solutions 26.0 software (IBM Corp., Armonk, NY, United States). The count data are expressed as numbers and were analyzed using χ^2 tests; the measurement data are expressed as the means ± SDs and were analyzed using independent samples *t* tests, and the collected data were normally distributed. A P value < 0.05 indicated statistical significance.

RESULTS

Patient enrollment and demographics (baseline characteristics and preoperative outcomes)

A total of 72 patients were eventually enrolled, and 4 patients were excluded from the study because of an intraoperative diagnosis of acute perforated appendicitis (n = 2), a postoperative pathologic diagnosis of a malignant tumor (n = 1), or midway withdrawal (n = 1). The patients' baseline demographics and preoperative clinical data are shown in Table 1. The patients' baseline data, including age, sex, body mass index, American Society of Anesthesiologists physical status classification[13], disease course, or preoperative outcomes, including VAS scores or inflammatory markers (WBC, NEU%, CRP and IL-6), did not significantly differ between the two groups, indicating strong comparability.

Postoperative clinical outcomes

As Table 2 shows, the 12- and 24-hour postoperative VAS scores fluctuated between 1 and 2 points in both groups, indicating a mild response, and the difference was not significant (P = 0.091). The first times to postoperative exhaust and out-of-bed activity fluctuated by approximately 20 and 15 hours, respectively, in both groups, and the differences were not significant (P = 0.41; P = 0.575, respectively). The 24-hour postoperative inflammatory marker levels, including WBC, NEU%, CRP, and IL-6 levels, did not significantly differ between the two groups (P = 0.419; P = 0.371, respectively). Similarly, the operative time, postoperative length of hospital stay and hospitalization cost were not significantly different between the two groups (P = 0.172; P = 0.664; P = 0.194, respectively). After the 1-month postoperative follow-up, no complications, including incision infection, hernia, abdominal abscess, or intestinal obstruction, were observed in either group.

DISCUSSION

Acute appendicitis is one of the most well-known causes of abdominal pain worldwide, and appropriately selected minimally invasive surgical protocols can reduce surgical trauma and psychologically burden for patients, resulting in a

Table 1 Baseline demographics and preoperative clinical data, mean ± SD

Variable	mSLAN group (*n* = 36)	CLA group (*n* = 36)	*P* value
Age, years	36.92 ± 15.4	38.08 ± 20.13	0.783
Sex, male/female	20/16	19/17	0.815
BMI, kg/m^2	23.86 ± 3.23	24.15 ± 4.4	0.748
ASA	1.5 ± 0.51	1.53 ± 0.51	0.817
Disease course, hours	21.39 ± 17.53	19.71 ± 17.04	0.681
Preoperative data			
WBC, × 10^9/L	12.42 ± 4.6	12.59 ± 4.75	0.877
NEU, %	80.33 ± 11.31	78.75 ± 10.95	0.549
CRP, μg/L	16.08 ± 24.63	19.53 ± 26.49	0.569
IL-6, ng/L	90.45 ± 301.61	95.41 ± 279.34	0.942
VAS scores	2.92 ± 0.28	2.89 ± 0.4	0.733

mSLAN: Modified single-port laparoscopic appendectomy using needle-type grasping forceps; CLA: Conventional three-port laparoscopic appendectomy; BMI: Body mass index; ASA: American Society of Anesthesiologists physical status; WBC: White blood cells; NEU: Neutrophil ratio; CRP: C-reactive protein; IL-6: Interleukin-6; VAS: Visual analog scale.

Table 2 Postoperative clinical outcomes between different surgical protocol groups, mean ± SD

Variable	mSLAN group (*n* = 36)	CLA group (*n* = 36)	*P* value
Postoperative 12-hour VAS scores	1.81 ± 0.58	1.94 ± 0.48	0.268
Postoperative 24-hour VAS scores	1.28 ± 0.45	1.47 ± 0.51	0.091
Postoperative 24-hour laboratory test outcomes			
WBC, × 10^9/L	9.18 ± 3.38	9.79 ± 3.72	0.465
NEU, %	73.8 ± 8.99	72.99 ± 10.35	0.725
CRP, mg/L	49.09 ± 36.51	58.43 ± 58.41	0.419
IL-6, pg/L	11.07 ± 17.22	15.66 ± 25.35	0.371
First postoperative exhaust time, hours	20.22 ± 8.62	22.24 ± 11.76	0.41
First out-of-bed activity time, hours	15.51 ± 6.39	16.38 ± 6.57	0.575
Operative time, minutes	38.67 ± 14.05	34.5 ± 11.44	0.172
Postoperative hospital stay, days	3.06 ± 1.13	3.17 ± 1.04	0.664
Cost of hospitalization, yuan	10776.75 ± 1117.8	10417.51 ± 1207.42	0.194

mSLAN: Modified single-port laparoscopic appendectomy using needle-type grasping forceps; CLA: Conventional three-port laparoscopic appendectomy; BMI: Body mass index; ASA: American Society of Anesthesiologists physical status; WBC: White blood cells; NEU: Neutrophil ratio; CRP: C-reactive protein; IL-6: Interleukin-6; VAS: Visual analog scale.

smooth recovery process[3,14]. Single-port laparoscopic appendectomy is an advanced minimally invasive surgery, and because upgraded instruments and equipment are used, good aesthetic outcomes can be achieved[15,16]. However, the size of the incision used in existing single-port approaches is approximately 1.5 to 2.5 cm[17,18], and this incision can be further improved for patients with high cosmetic requirements. Moreover, the surgical difficulties caused by the parallel operation relationship of single-port laparoscopic surgery urgently need solutions. Notably, the selection of the surgical technique should be tailored to each patient's unique circumstances, the surgeon's expertise, and the patient's preferences [19]. Patients with acute uncomplicated appendicitis tend to prefer a single-port laparoscopic protocol that is less traumatic and characterized by wide surgical fields and a high level of patient comfort. Technical advancements are needed to ensure that patients receive the most effective and safest care possible.

In recent years, we have continuously modified surgical procedures and updated surgical instruments to improve surgeon comfort, increase surgical safety, and expand surgical indications. The aim of this prospective study was to demonstrate the feasibility, safety, effectiveness, and clinical application potential of the mSLAN protocol by comparing

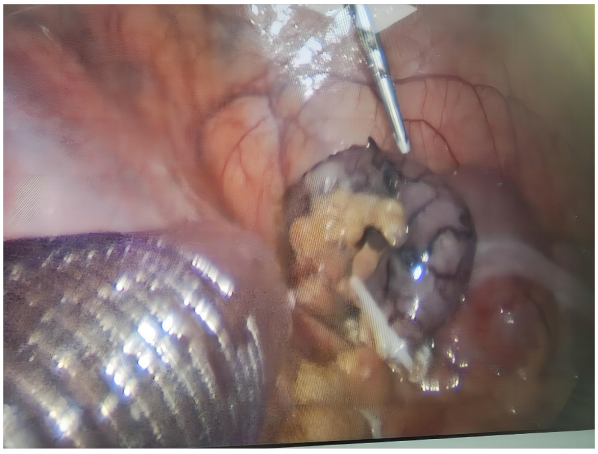


Figure 1 The 10 mm trocar was observed in the surgical fields.



Figure 2 Surgical incision appearance. A: Intraoperative surgical incision appearance of modified single-port laparoscopic appendectomy using needle-type grasping forceps (mSLAN); B: Intraoperative surgical incision appearance of conventional three-port laparoscopic appendectomy; C: Postoperative 1-month surgical incision appearance of mSLAN.

the short-term clinical outcomes with those of the CLA protocol.

A mild postoperative pain response and early out-of-bed activity were observed in both groups

Pain at the surgical incision is one of the most common surgical complications. As minimally invasive surgical techniques have gradually replaced laparotomies, smaller incisions are associated with less postoperative pain and therefore more manageable physical and psychological burdens. Moreover, the length of the incision made for the mSLAN procedure in our center was smaller than that made for the CLA procedure (1.5 cm *vs* 2.7 cm); however, does this modification lead to less postoperative pain?

The VAS is commonly used to score pain intensity. Scores range from 0 to 10; a score of 0 indicates no pain, a score less than 3 points indicates tolerable pain, and a score of 10 indicates severe pain[11]. Previous studies have suggested that single-port laparoscopic surgery may be associated with severe postoperative pain[20]; however, we noted low postoperative VAS scores in both groups, indicating mild pain. Although the 12- and 24-hour postoperative VAS scores and the times to first out-of-bed activity were not significantly different between patients who underwent the mSLAN procedure and those who underwent the CLA procedure, the less intense pain associated with this novel technique was sufficient for it to gain acceptance.

The mSLAN protocol induced a similar inflammatory response and had a similar cost and recovery process to those of CLA

Postoperative inflammation is well known to slow the recovery process and cause a series of complications, such as fever, incision infection, and ileus. The inflammatory response after appendectomy can be caused by appendicitis or surgical trauma. In this study, we evaluated the inflammatory response after appendectomy *via* an integrated analysis of inflammatory markers, including WBC, NEU%, CRP and IL-6.

As stated in previous studies, single-port laparoscopic surgery may result in more severe surgical trauma and elevated levels of inflammatory markers, such as IL-6 and CRP, postoperatively[20]. Nevertheless, the levels of inflammatory

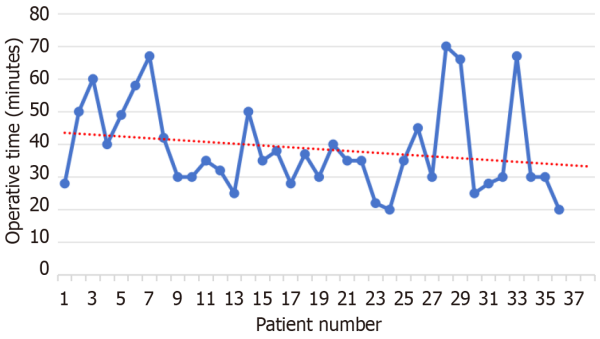


Figure 3 Operative time evolution trends in modified single-port laparoscopic appendectomy using needle-type grasping forceps group.

biomarkers (WBC, NEU%, CRP and IL-6) before and after surgery did not significantly differ. As a novel technical protocol, the modified SLAN procedure is safe; does not cause considerable surgical trauma, postoperative inflammatory responses, or postoperative infectious complications; and is not associated with a slow recovery (3.06 days *vs* 3.17 days). In addition, needle-type grasping forceps were supported by our project fund, whereas other traditional surgical instruments do not incur additional hospital costs. Considering the similar postoperative hospital stay durations for the two procedures, the hospitalization cost increased only slightly (10776.75 yuan *vs* 10417.51 yuan).

Postoperative recovery of gastrointestinal function was comparable

Postoperative gastrointestinal function recovery is a source of concern after abdominal surgery. Early gastrointestinal function recovery can facilitate early oral feeding and promote enhanced recovery after surgery and even early discharge [21]. Postoperative gastrointestinal dysfunction is associated with inflammation, surgical trauma and stress, as mentioned previously. This study revealed no significant differences between the two groups in terms of the time to first postoperative exhaust (20.22 hours *vs* 22.24 hours), indicating that the recovery of postoperative gastrointestinal function was comparable, which may be related to similar postoperative inflammatory responses and times to first out-of-bed activity.

A significant decrease in the surgical time was observed in the mSLAN group

The surgical duration reflects not only the severity of the disease and the complexity of the surgery but also the popularity of the surgical protocol. According to previous studies[20,22,23], the long duration of single-port appendectomy may be closely related to the parallel operative angle of single-port surgery, which limits the generalizability of this technique. Although the initial SLAN protocol calls for a substantially smaller surgical incision, the use of two 5 mm caliber trocars limits the applicability of the procedure in patients with severe edema and appendicitis, precludes the insertion of long Ham-o-lock clips, leads to instability in the pneumoperitoneum pressure, and prevents aseptic smooth removal of the specimen, resulting in a long, limited, unsafe procedure.

Unlike in the initial SLAN protocol, a 1.5 cm umbilical incision was used in the modified protocol, a CO_2 pneumoperitoneum was routinely established, and two trocars (10 mm and 5 mm caliber) were used to maintain stable pneumoperitoneum pressure. In particular, the substitution of a 10 mm trocar allowed the convenient placement of long ham-o-lock clips and gauze into the abdominal cavity. The procedure used to remove the appendix was the same as that used in the CLA, ensuring an aseptic and safe procedure, shortening the surgical time and expanding the surgical indications. Notably, the 10 mm trocar was moved forward from the right iliac fossa intraoperatively, thus avoiding obstructing the laparoscopic view of the CO_2 pneumoperitoneum and preventing instrument collision due to poor cooperation between the surgeon and assistant during surgery. Thus, the surgical procedure was safer and smoother.

Our study revealed that the mean surgical time was significantly shorter in the mSLAN group than in the traditional SLAN group (38.67 minutes *vs* 66.25 minutes)[9] and tended to decrease, suggesting that surgeons were gradually mastering the technique (Figure 3).

In addition, the new SLAN protocol was modified to be more efficiently converted to the CLA protocol. For example, one patient was intraoperatively diagnosed with acute perforated appendicitis, and the mSLAN protocol was discontinued. Subsequently, incisions were made at the McBurney and converse McBurney sites; thus, no additional surgical incisions were needed, thereby maintaining the surgical duration.

In summary, the short-term outcomes of the CLA protocol and the modified SLAN protocol were comparable. Through improvements in the technical protocol and the application of a 10 mm trocar and disposable bag, the pneumoperitoneum pressure was effectively maintained, the surgical space was sufficiently increased, the surgical duration was greatly reduced, the surgical indications were expanded, and the incidence of postoperative complications was significantly reduced. Although the size of the umbilical incision was increased to 1.5 cm compared with that of the initial protocol, the cosmetic effect was not inferior (Figure 2A); moreover, the cosmetic effect at 1 month after surgery remained favorable (Figure 2C). The mSLAN protocol has high potential for clinical application and generalization, especially for patients with high cosmetic requirements. Our technical protocol and present study have several limitations. First, the needle-type grasping forceps are soft and easy to twist (Figure 4). Second, the abdominal drainage tube cannot be placed during single-port surgery, and surgeons should promptly switch to three-port surgery if severe disease is identified in the abdomen. Third, our study is a single-blinded, small-sample, single-center study, which may introduce subjective bias in terms of outcomes such as pain scores and potentially impact the detection of postoperative



Figure 4 Needle-type grasping forceps with a twisted head. The soft texture of needle-type grasping forceps is easy to twist.

complications; moreover, the rates of long-term complications, such as incisional hernias and adhesive intestinal obstructions, are unclear. Thus, additional studies with double-blinded, larger sample sizes conducted at multiple centers with long-term follow-up results are needed to evaluate long-term clinical outcomes and increase statistical power.

CONCLUSION

The CLA protocol and the modified SLAN protocol had comparable short-term clinical outcomes as well as similar surgical durations and better cosmetic outcomes; thus, the modified SLAN protocol has notable clinical application potential and superiority for patients with high cosmetic requirements. In the future, long-term clinical outcomes need to be evaluated, and more practical and reliable surgical instruments need to be designed and developed.

FOOTNOTES

Author contributions: Chen Y and Guo SG contributed to conception and design; Chen Y contributed to surgical protocol modified and performed, and manuscript writing; Fu XA, Fan ZQ, Zhang XX, Liu H, Liu Z, and Huang YS contributed to study materials provision, data collection and analysis; Yuan JQ and Song L contributed to patient care, follow up and literature search and selection; All authors reviewed and approved the final manuscript.

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ORIGINAL ARTICLE

Basic Study

Single-nucleus RNA sequencing and spatial transcriptomics reveal the mechanism by which Xiaozhiling injection treats internal hemorrhoids

Min-Hui Ke, Shu-Yan Huang, Wei-Gan Lin, Zhen-Guo Xu, Xia-Xia Zheng, Xian-Bao Liu, You-Min Cheng, Zuan-Fang Li

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Abstract

BACKGROUND

Hemorrhoids, a prevalent chronic condition globally, significantly impact patients' quality of life. While various surgical interventions, such as external stripping and internal ligation, procedure for prolapse and hemorrhoids, and tissue selecting technique, are employed for treatment, they are often associated with postoperative complications, including unsatisfactory defecation, bleeding, and anal stenosis. In contrast, Xiaozhiling injection, a traditional Chinese medicine-based therapy, has emerged as a minimally invasive and effective alternative for internal hemorrhoids. This treatment offers distinct advantages, such as reduced dietary restrictions, broad applicability, and minimal induction of systemic inflammatory responses. Additionally, Xiaozhiling injection effectively eliminates hemorrhoid nuclei, prevents local tissue necrosis, preserves anal cushion integrity, and mitigates postoperative complications, including bleeding and prolapse. Despite its clinical efficacy, the molecular mechanisms underlying its therapeutic effects remain poorly understood, warranting further investigation.

AIM
To investigate the molecular mechanism underlying the therapeutic effect of Xiaozhiling injection in the treatment of internal hemorrhoids.

METHODS
An internal hemorrhoid model was established in rats, and the rats were randomly divided into a modeling group [control group (CK group)] and a treatment group. One week after injection, Stereo-seq and electron microscopy were used to study the changes in gene expression and subcellular structures in fibroblasts.

RESULTS
Single-cell sequencing revealed differences in the expression and transcript levels of the genes collagen 3 alpha 1, decorin, and actin alpha 2 in fibroblasts between the CK group and the treatment group. Spatial transcriptome analysis revealed that genes of the sphingosine kinase 1 (Sphk1)/sphingosine-1-phosphate (S1P) pathway spatially overlapped with key genes of the transforming growth factor beta 1 pathway, namely, *Sphk1*, S1P receptor, and transforming growth factor beta 1, in the treatment group. The proportion of fibroblasts was lower in the treatment group than in the CK group, and Xiaozhiling treatment had a significant effect on the proportion of fibroblasts in hemorrhoidal tissue. Immunohistochemistry revealed a significant increase in the expression of a fibroblast marker. Electron microscopy showed that the endoplasmic reticulum of fibroblasts contained a large amount of glycogen, indicating cell activation. Fibroblast activation and the expression of key genes of the Sphk1-S1P pathway could be observed at the injection site, suggesting that after Xiaozhiling intervention, the Sphk1-S1P pathway could be activated to promote fibrosis.

CONCLUSION
Xiaozhiling injection exerts its therapeutic effects on internal hemorrhoids by promoting collagen synthesis and secretion in fibroblasts. After Xiaozhiling intervention, the Sphk1-S1P pathway can be activated to promote fibrosis.

Key Words: Internal hemorrhoids; Xiaozhiling injection; Fibroblast; Marker gene; Single-cell sequencing; Spatial transcriptome sequencing

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Core Tip: Single-cell sequencing revealed differences in the expression and transcription levels of genes collagen 3 alpha 1, decorin, and actin alpha 2 in fibroblasts between the control groups and treatment groups. The activation of fibroblasts and the expression of key genes in the sphingosine kinase 1-sphingosine-1-phosphate pathway were observed at the injection site, suggesting that the sphingosine kinase 1-sphingosine-1-phosphate pathway could be activated to promote fibrosis after the intervention of Xiaozhling.

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INTRODUCTION

Hemorrhoids are a common chronic condition worldwide that affects people's lives. There are many surgical methods for the treatment of hemorrhoids, including external stripping and internal ligation, the procedure for prolapse and hemorrhoids, and the tissue selecting technique, but these treatments are associated with postoperative complications of different severities, such as unsatisfactory defecation, bleeding, and anal stenosis[1,2]. Due to the anatomy of the rectum and the pathogenesis of hemorrhoids, Xiaozhiling injection is the main treatment for internal hemorrhoids in Chinese medicine. Xiaozhiling injection has clear advantages in the treatment of hemorrhoids as well as a curative effect. It is less invasive and requires less dietary restrictions than other treatments, and it is widely applicable, does not induce a strong systemic inflammatory response, and causes acute inflammation for only a short period of time. It can eliminate the hemorrhoid nucleus, prevent local tissue necrosis, protect and fix the anal cushion, and reduce complications and sequelae such as postoperative bleeding and prolapse[3].

Since its discovery more than 40 years ago, Xiaozhiling injection has been widely used in China and more than 50 other countries and regions, such as Japan and South Korea[4]. Aluminum potassium sulfate and tannic acid (ALTA) injection, which is an improved version of Xiaozhiling, is widely used in Japan. Xiaozhiling injection[5] has good clinical efficacy

and high safety in the treatment of grades II-III internal hemorrhoids and can significantly alleviate the symptoms of hematostoecium and prolapse in patients with internal hemorrhoids; moreover, the amount of time and hospital stay required for treatment are short, and it is associated with few and mild postoperative complications. To date, studies on the mechanism underlying the effect of Xiaozhiling have focused on its impact on aseptic inflammation and tissue fibrosis [4], which mainly involves functional changes in fibroblasts. Fibroblasts are normally located in the tissue interstitium and play a key role in maintaining tissue structural integrity, healing, and regeneration[6]. In normal colorectal tissues, fibroblasts are evenly distributed in the lamina propria adjacent to the colorectal mucosal epithelium and in tissues and organs rich in epithelial cells, and secreted collagen and lamin form elastic and viscous tissue structures[7]. Owing to the wide distribution of fibroblasts and their diverse functions, fibroblast activation is considered the key to tissue fibrosis[8, 9]. Fibroblasts can secrete cytokines, chemokines, *etc.* to modify the intensity and duration of the inflammatory response. They can also release interleukin-1β and transforming growth factor-β (TGF-β) to promote the differentiation of fibroblasts into myofibroblasts (Myofs) under the influence of mechanical tension[10]. Through immunohistochemical analysis, Sferra *et al*[11] found that the expression of TGF-β1 and sphingosine kinase-1 (Sphk1) was elevated in the intestinal mucosa and submucosa of mice with colorectal fibrosis, suggesting that the TGF-β1-mediated Sphk1-sphingosine 1-phosphate (S1P) signaling pathway could facilitate Myof activation and result in fibrosis.

In a previous study, our research group found that the thickness of the submucosal tissue in the hemorrhoidal area changed and fibroblasts proliferated after Xiaozhiling treatment, suggesting that the drug induced some changes in the cell population; however, changes in various cells and the spatial pattern of Sphk1-S1P signaling pathway activation at the single-cell level were not assessed. This study was designed to explore the complexity and diversity of pathophysiological changes by combining multiple types of molecular data and spatial information through single-cell sequencing and spatial transcriptome profiling, starting from the spatial distribution of genes in hemorrhoidal tissues. Spatiotemporal omics technology can be used to assess the spatiotemporal distributions of various cell types, the proportions of these cell types, the molecular interactions among cells, gene expression in different types of cells to obtain an accurate map, and thus provide a reference for exploring the occurrence and development of diseases and the mechanism of action of drugs[12]. In this study, the spatial distribution and transcript levels of key genes in the Sphk1-S1P and TGF-β1 pathway, namely *Sphk1*, S1P receptor 1 (*S1PR1*), and *TGF-β1*, after Xiaozhiling injection were evaluated. The results demonstrated that Xiaozhiling injection could activate the Sphk1-S1P pathway to promote fibrosis.

MATERIALS AND METHODS

Experimental drugs and reagents

Xiaozhiling injection (Beijing China Resources High-Tech Natural Medicine Co., Ltd.); inhaled isoflurane (Baxter Healthcare Corporation, China); 4% neutral formaldehyde fixative solution; 6% croton oil (Beijing Huawei Ruike Chemical Co., Ltd.); pyridine (Beijing Lambolide Trading Co., Ltd.); ether (Xilong Science Co., Ltd.); horseradish peroxidase-conjugated polyclonal anti-rabbit/mouse IgG (Boster); an anti-TGF-β1 rabbit polyclonal antibody (Proteintech); an anti-Sphk1 rabbit polyclonal antibody (Proteintech); an anti-sphingosine-1-phosphate receptor 1 (S1PR1) rabbit polyclonal antibody (Proteintech); and an alpha smooth muscle actin specific monoclonal antibody (Proteintech) were used in this study.

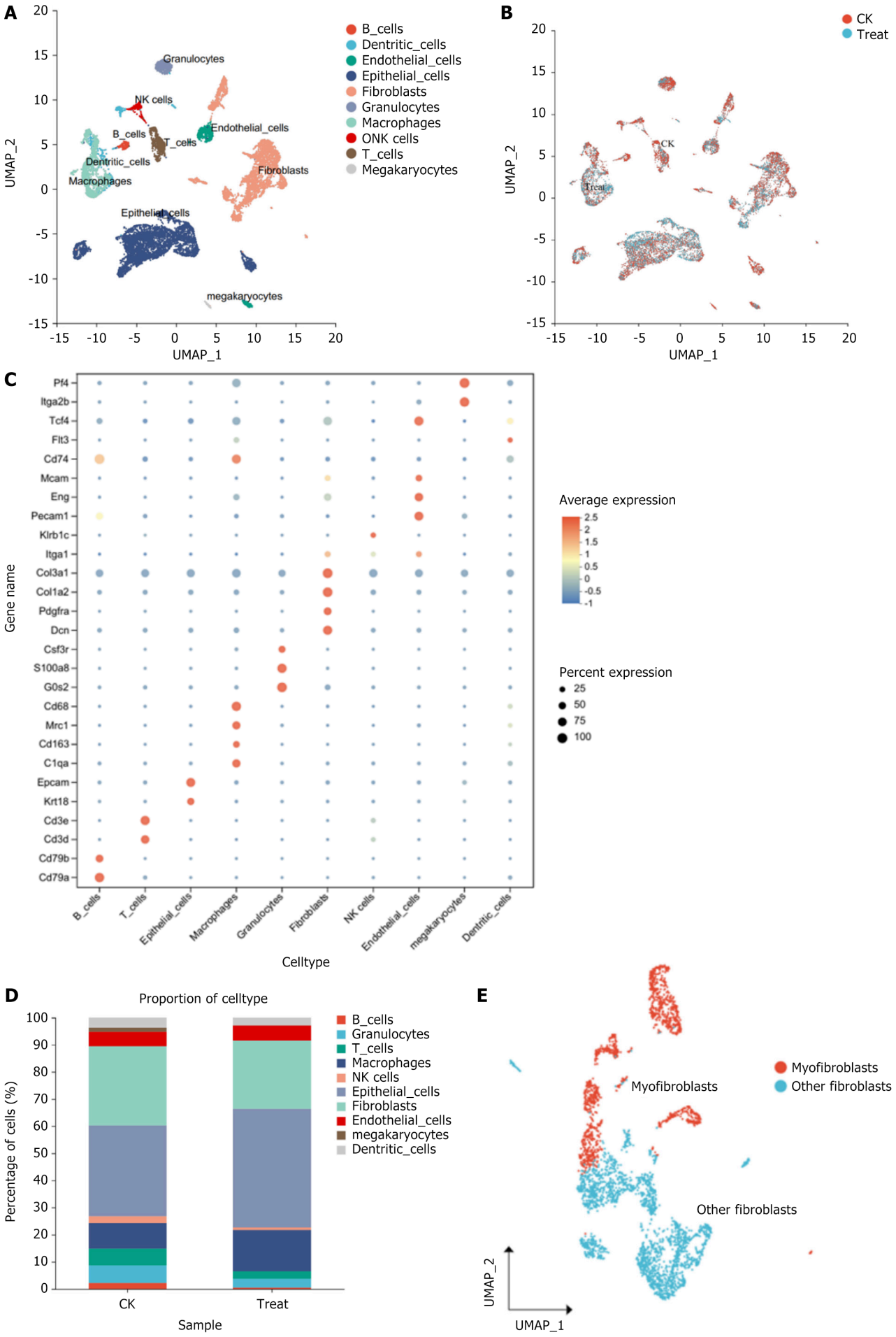
Experimental animals and groups

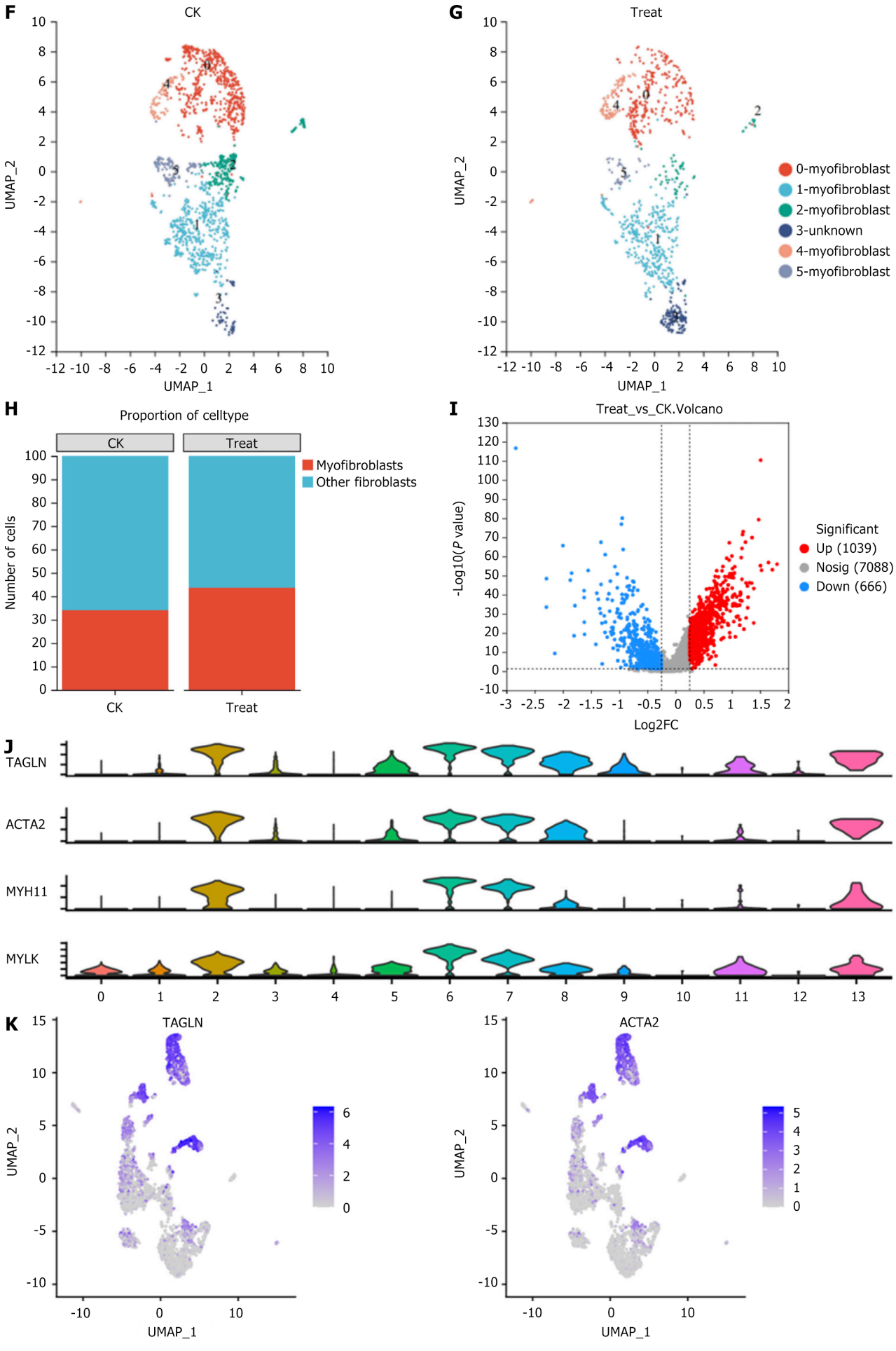
A total of 20 healthy specific pathogen-free 8-week-old male SD rats weighing 180-220 g were purchased from SCXK Laboratory Animal Co., Ltd. (Shanghai; 2018–0004). The animals were raised in the Laboratory Animal Center of Fujian University of Chinese Medicine [approval No. SYXK (Fujian) 2019-0007]. Standard food was provided by the Laboratory Animal Center of Fujian University of Chinese Medicine. The animals were housed on a 12-hour light/dark cycle at a constant humidity and controlled temperature of 22-25 °C. The experiments were carried out after 1 week of adaptation. All operations were performed in accordance with the ethics requirements of the Fujian Academy of Traditional Chinese Medicine (approval No. FJATCM-IAEC2018015). The rats were treated in accordance with the Guiding Opinions on the Kindness of Laboratory Animals[13]. Twenty rats were randomly divided into a control group (CK group) and a treatment group (10 rats in each group) after the internal hemorrhoid model was successfully established as previously described[14].

RESULTS

Single-nucleus RNA sequencing

To investigate the differences in the expression and transcript levels of classic fibroblast marker genes in the hemorrhoidal region, single-cell transcriptome sequencing of hemorrhoidal tissue was performed 1 week after model establishment. According to the results of single-cell transcriptome sequencing, a total of 12589 high-quality cells were obtained; there were 7538 cells from the modeling group (CK group), with a median gene number of 1738, and 5051 cells from the Xiaozhiling (treatment group), with a median gene number of 2174. A total of 29 cell clusters were identified using Seurat software for reduction and visualization, and these clusters were found to consist of the following 10 cell types on the basis of the expression of classic markers: B cells, dendritic cells, endothelial cells, epithelial cells, fibroblasts, granulocytes, macrophages, neurons, T cells, and megakaryocytes (Figure 1A). The cell types present in the CK group


A
B_cells
Dentritic_cells
Endothelial_cells
Epithelial_cells
Fibroblasts
Granulocytes
Macrophages
ONK cells
T_cells
Megakaryocytes
Granulocytes
NK cells
B_cells
T_cells
Endothelial_cells
Dentritic_cells
Fibroblasts
Macrophages
Epithelial_cells
megakaryocytes
UMAP_1
UMAP_2
B
CK
Treat
C
Gene name
Celltype
Average expression
Percent expression
D
Proportion of celltype
Percentage of cells (%)
Sample
CK
Treat
E
Myofibroblasts
Other fibroblasts
UMAP_1
UMAP_2


F
CK
UMAP_2
UMAP_1
G
Treat
0-myofibroblast
1-myofibroblast
2-myofibroblast
3-unknown
4-myofibroblast
5-myofibroblast
H
Proportion of celltype
CK
Treat
Number of cells
Myofibroblasts
Other fibroblasts
I
Treat_vs_CK.Volcano
-Log10(P value)
Log2FC
Significant
Up (1039)
Nosig (7088)
Down (666)
J
TAGLN
ACTA2
MYH11
MYLK
K
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ACTA2
UMAP_1
UMAP_2

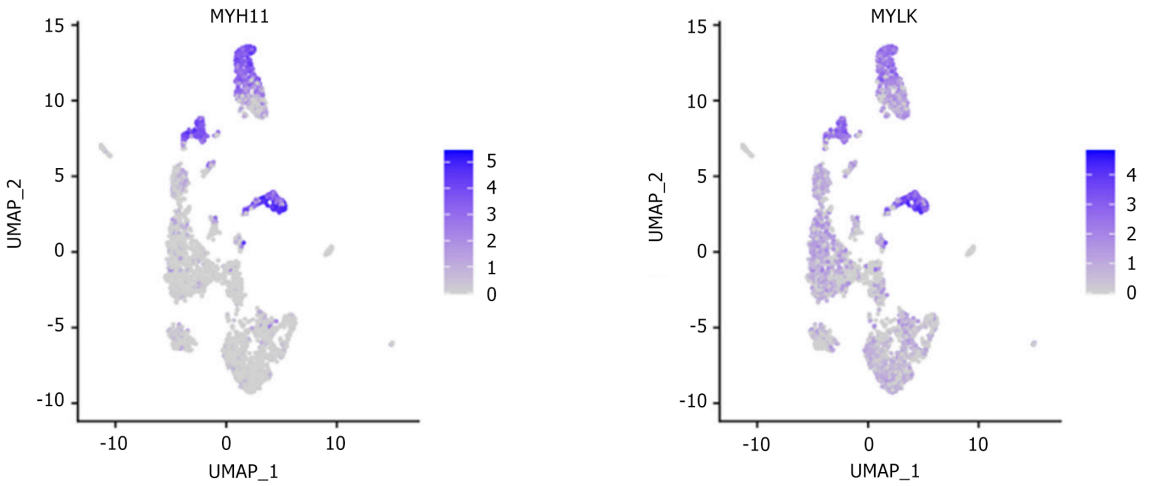


Figure 1 Single-cell transcriptome map. A: Uniform manifold approximation and projection (UMAP) of cell types, with different colors representing different cell types; B: Visualization of cell dimension reduction in the modeling group and Xiaozhiling group, with different colors representing different groups; C: Bubble map of classic marker genes in each cell type; D: Cell proportion diagrams for the model group and Xiaozhiling group, with different colors representing different clusters; E: Analysis of large groups of differentially expressed genes in fibroblasts; F: UMAP of fibroblasts; G: UMAP of Xiaozhiling-treated fibroblasts; H: Proportions of fibroblasts in different groups; I: Volcano plot of differentially expressed genes (actin alpha 2, myosin heavy chain 1, myosin light chain kinase, and transgelin) in fibroblasts; J: Violin plot of classic fibroblast markers in each cluster; K: UMAP of classic fibroblast markers. UMAP: Uniform manifold approximation and projection; NK: Natural killer; TAGLN: Transgelin; ACTA2: Actin alpha 2; MYH11: Myosin heavy chain 1, MYLK: Myosin light chain kinase; CK: Control group.

and treatment group were essentially the same (Figure 1B). Bubble maps of marker genes of each cell type are shown in Figure 1C. There were significant differences in the proportions of the different cell types between the two groups (Figure 1D-G), and the proportion of Myofs cells in the Xiaozhiling group significantly increased (Figure 1H and I). Gene display of the large groups of differentially expressed genes in fibroblasts and smaller cell clusters revealed that the expression of classic marker genes of Myofs (actin alpha 2, myosin heavy chain 11, myosin light chain kinase, and transgelin) changed (Figure 1J and K). These findings suggested that Myof proliferation was stimulated after drug intervention.

The spatial expression patterns of *Sphk1*, *S1PR1*, and *TGF-β1*, key genes of the Sphk1-S1P and TGF-β1 pathways, after Xiaozhiling injection were analyzed. Since single-cell transcriptome sequencing revealed differences in the transcriptome of fibroblasts before and after intervention, spatial transcriptome sequencing was performed to further explore changes in the spatial location of fibroblasts and to determine whether there is a relationship between the TGF-β1 pathway and the spatial location of fibroblasts. The spatial localization of cell types in internal hemorrhoid tissue was analyzed *via* spatial transcriptome sequencing. The total number of genes expressed in internal hemorrhoid tissue (Figure 2A and B) was 17590, with the median number of genes being 4943; the total number of genes expressed in hemorrhoid tissue one week after Xiaozhiling injection was 17792 (Figure 3A and B), with the median number of genes being 5980. The differences in the expression of classic fibroblast marker genes (collagen 3 alpha 1, decorin, and actin alpha 2) in tissues before and after drug intervention were subsequently explored (Figure 2C and Figure 3C), as were the spatial localization of these genes (Figure 2D and Figure 3D). The expression levels of fibroblast marker genes after drug intervention were significantly greater than those before intervention. The spatial localization of key genes of the Sphk1-S1P and TGF-β1 pathways, *i.e.*, *Sphk1*, *S1PR1*, and *TGF-β1*, was assessed (Figure 2E and Figure 3E). The expression levels of Sphk1-S1P and TGF-β1 pathway-related genes (Figure 2F, Figure 3F and G) were significantly increased in areas where fibroblasts were concentrated after Xiaozhiling injection. These findings suggest that the Sphk1-S1P pathway is activated after the injection of Xiaozhiling.

Transmission electron microscopy

According to spatiotemporal omics localization and transmission electron microscopy, the endoplasmic reticulum of fibroblasts was obviously active, and the endoplasmic reticulum was rich in glycogen. These findings suggest that the fibroblasts were activated after Xiaozhiling injection, which is consistent with the spatiotemporal omics results (Figure 4).

Immunohistochemistry

Changes in the expression of the Sphk1-S1P signaling pathway-related proteins Sphk1, S1PR1, and TGF-β1 before and after injection were detected *via* immunohistochemistry. Tissues were collected from the hemorrhoidal area before and after drug intervention, and the changes in the expression of the Sphk1-S1P signaling pathway-related proteins Sphk1, S1PR1, and TGF-β1 before and after injection were detected *via* immunohistochemistry. According to the immunohistochemical staining results, the submucosal thickness increased significantly, and the expression of Sphk1, S1PR1, and TGF-β1, and other related indicators increased after Xiaozhiling injection, indicating that the Sphk1-S1P signaling pathway was activated. These results are consistent with the spatial transcriptome data (Figures 5 and 6).

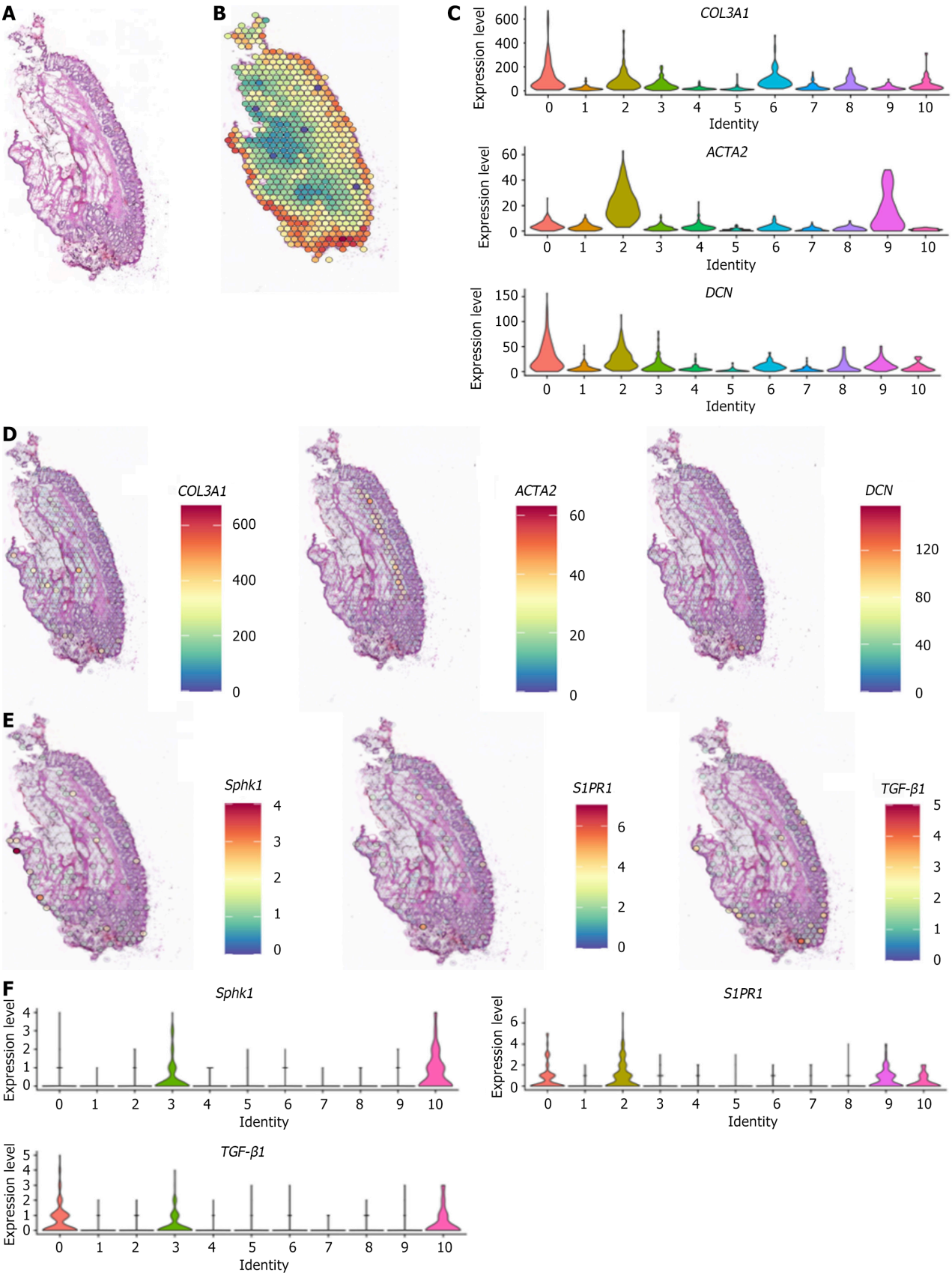
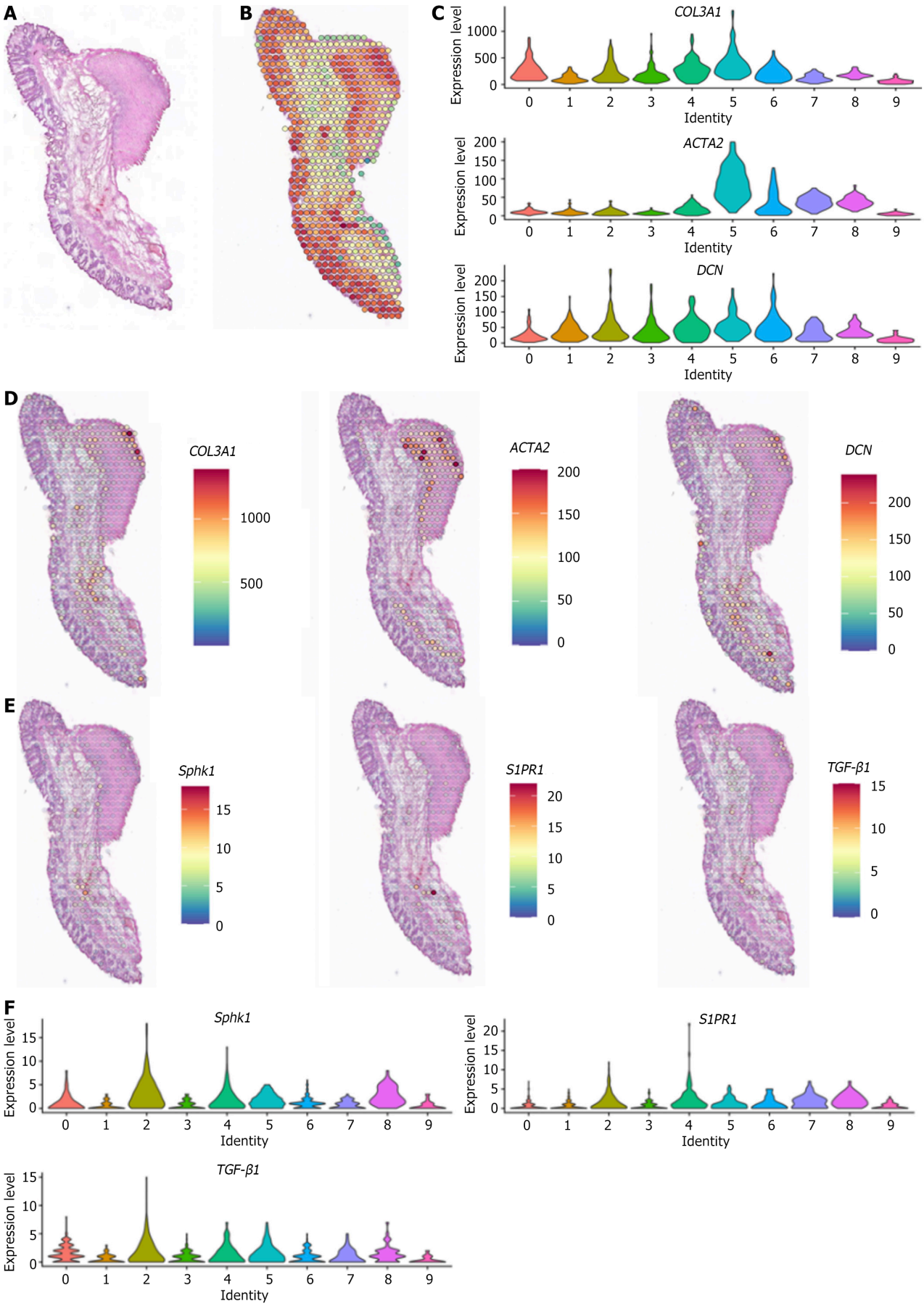


Figure 2 Spatial transcriptome map of internal hemorrhoid tissue. A: Hematoxylin and eosin-stained section of internal hemorrhoid tissue; B: Spatial transcriptome; C: Differences in expression of the classic marker genes collagen 3 alpha 1, decorin, and actin alpha 2 in fibroblasts; D: Spatial localization of the classic marker genes collagen 3 alpha 1, decorin, and actin alpha 2 in fibroblasts; E: Spatial distribution of sphingosine kinase 1, sphingosine-1-phosphate receptor 1, and transforming growth factor-β1; F: Differences in gene expression of sphingosine kinase 1, sphingosine-1-phosphate receptor 1, and transforming growth factor-β 1. *COL3A1*: Collagen 3 alpha 1; *DCN*: Decorin; *ACTA2*: Actin alpha 2; *Sphk1*: Sphingosine kinase 1; *S1PR1*: Sphingosine-1-phosphate receptor 1; *TGF-β1*: Transforming growth factor-β1.


A
B
C
COL3A1
ACTA2
DCN
Expression level
Identity
D
COL3A1
ACTA2
DCN
E
Sphk1
S1PR1
TGF-β1
F
Sphk1
S1PR1
TGF-β1

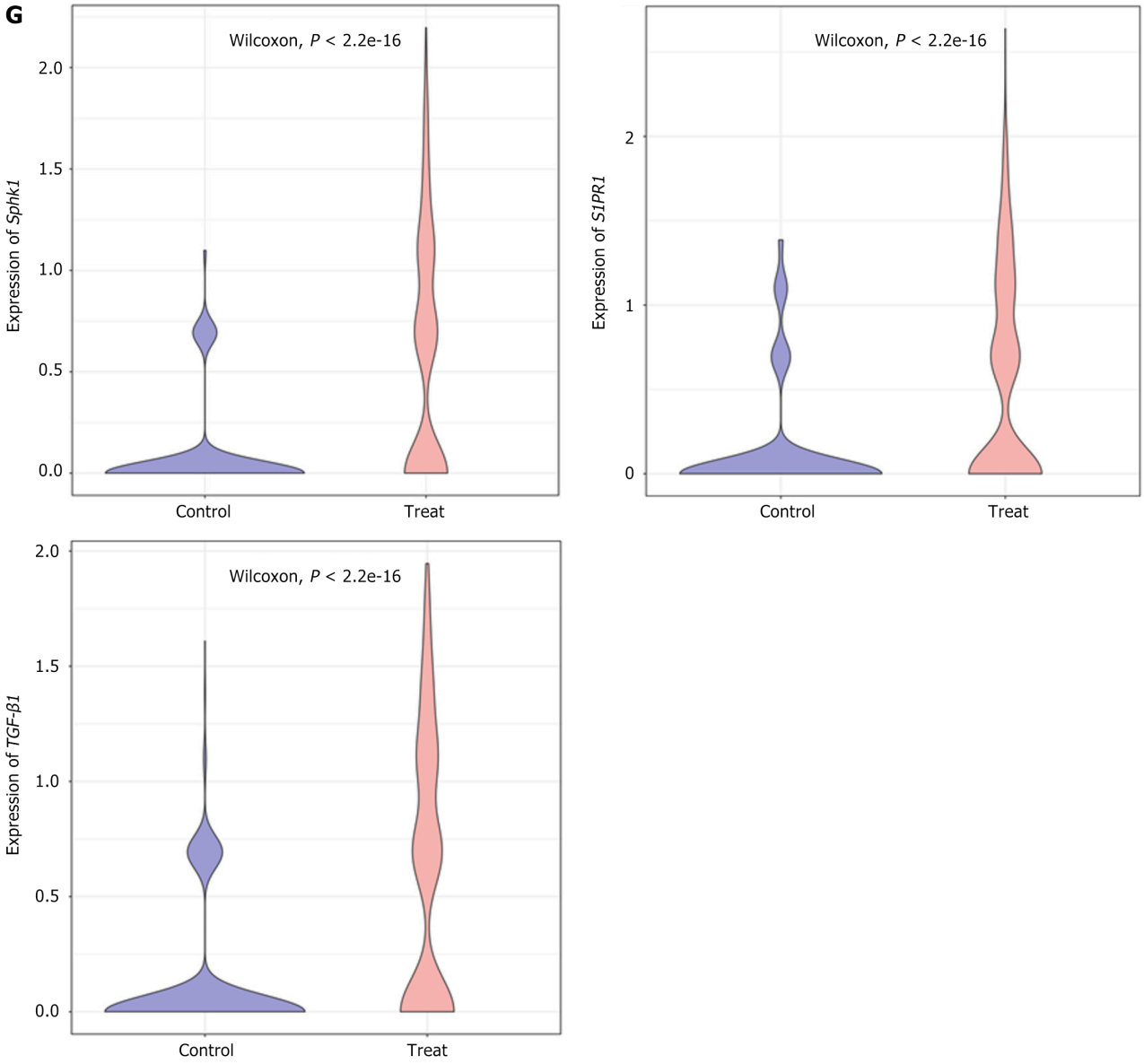


Figure 3 Spatial transcriptome. A: Hematoxylin and eosin-stained section 1 week after Xiaozhiling injection; B: Spatial transcriptome; C: Differences in expression of the classic fibroblast marker genes collagen 3 alpha 1, decorin, and actin alpha 2 in different clusters; D: Spatial localization of the classic fibroblast marker genes collagen 3 alpha 1, decorin, and actin alpha 2; E: Spatial localization of sphingosine kinase 1, sphingosine-1-phosphate receptor 1, and transforming growth factor-β1; F: Differences in expression of sphingosine kinase 1, sphingosine-1-phosphate receptor 1, and transforming growth factor-β1 in different clusters; G: Analysis of differences between the two groups. *COL3A1*: Collagen 3 alpha 1; *DCN*: Decorin; *ACTA2*: Actin alpha 2; Sphk1: Sphingosine kinase 1; S1PR1: Sphingosine-1-phosphate receptor 1; TGF-β1: Transforming growth factor-β1.

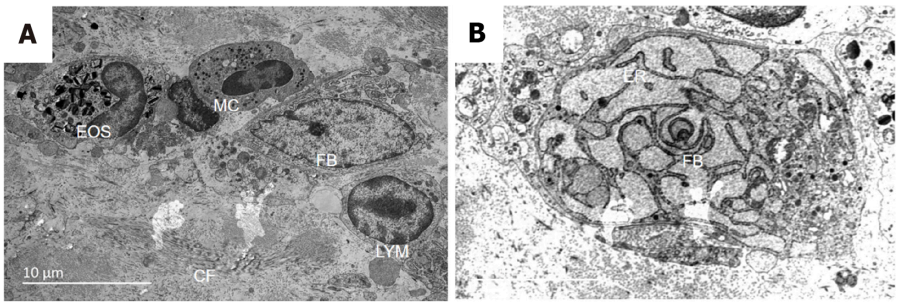


Figure 4 Transmission electron microscopy. A: Transmission electron microscopy (× 5000) of eosinophils, mast cells, fibroblasts, lymphocytes, and fiber bundles 1 week after Xiaozhiling injection treatment; B: Transmission electron microscopy (× 10000) of active endoplasmic reticulum of fibroblasts 1 week after Xiaozhiling injection, with abundant glycogen attached to the endoplasmic reticulum. EOS: Eosinophil; MC: Mast cell; FB: Fibroblast; LYM: Lymphocyte; CF: Fiber

bundles.

Immunofluorescence

Immunofluorescence staining suggested that alpha-smooth muscle actin (α-SMA) became highly expressed after Xiaozhiling injection (Figure 7).

Effects of Xiaozhiling on Sphk1-S1P pathway-related proteins in rat rectal tissue

Compared with the CK group, the protein expression of Sphk1, TGF-β1, and S1PR1 in the rectal tissue of the treatment group was significantly elevated ($P < 0.05$) (Figure 8).

DISCUSSION

Renowned experts in anorectal diseases applied the traditional Chinese medicine principle that "acid can be convergent, and astringency can be fixed", and selected gallnut and alum, which possess both sour and astringent properties, to formulate Xiaozhiling. ALTA injection, widely used in Japan, is a modified version of Xiaozhiling. Japanese researchers extracted tannic acid and aluminum potassium sulfate from traditional Chinese medicine to serve as the primary components in the preparation of this medication.

Spatiotemporal transcriptomics analysis has been widely used in the medical field. Qin *et al*[15] used single-cell RNA sequencing and spatial transcriptome sequencing technologies to characterize the heterogeneity and spatial structure of rectal cancer tissue. The study of cell dynamics in 29 colorectal cancer patients *via* this technique suggested that adjuvant chemotherapy can modulate the tumor microenvironment by reshaping cancer-associated fibroblast populations. Chen *et al*[16] used this technology to study the mechanism by which Buzhong Yiqi decoction alleviates rectal prolapse and reported that the expression of mouse platelet-derived growth factor A and mouse platelet-derived growth factor B in smooth muscle cells, pericytes, and fibroblasts in the treatment group was higher than that of the control group. Using this technique, researchers can identify temporal and spatial changes in cell populations, track the precise location of each cell, and determine how cells contribute to the development of disease and the effects of drug interventions over time.

To explore the effects of drug intervention on spatial gene expression patterns, spatial transcriptomics was used to analyze the spatial distribution of genes related to the Sphk1-S1P signaling pathway before Xiaozhiling injection and 1 week after intervention. 10 × Visium spatial transcriptome sequencing and corresponding single-cell RNA sequencing were used to characterize heterogeneity and differences in spatial structure before and after tissue intervention and to explore the mechanism of spatial-temporal changes in detail. Specifically, through single-cell spatial omics technology, we used 10 × Visium spatial transcriptome sequencing and 10 × single-cell RNA sequencing to reveal the heterogeneity of the cell populations and spatial gene expression patterns in internal hemorrhoid tissues before and after Xiaozhiling injection and explored the potential mechanism by which Xiaozhiling injection inhibits the progression of internal hemorrhoids.

There were changes in various parameters at different time points after Xiaozhiling injection; specifically, the thickness of the submucosa was the highest one week after drug intervention and then gradually decreased, suggesting that the transition period of inflammation and fibrosis may be one of the key turning points. In addition, the endoplasmic reticulum of fibroblasts was active and rich in glycogen, as observed *via* transmission electron microscopy. Therefore, one week after Xiaozhiling injection, single-cell and spatial omics experiments were performed. Notably, the proportion of fibroblasts in the Xiaozhiling group was lower than that of the model group, but the proportion of inflammatory cells was greater in the Xiaozhiling group than in the model group. Considering that inflammation occurred within one week after drug intervention, fibroblasts did not rapidly proliferate temporarily in this period. In the model group, there were 1507 Myofs, while in the Xiaozhiling group, there were 837 Myofs. These results indicated that Xiaozhiling had a significant effect on the proportion of fibroblasts in hemorrhoidal tissue but that the rapid proliferation of fibroblasts did not occur one week after drug intervention. On the basis of the above studies, it is currently speculated that TGF-β1 can significantly upregulate the expression of the *Sphk1* gene and protein in fibroblasts and that the mechanism by which Xiaozhiling induces fibrosis is related to the Sphk1-S1P signaling pathway.

TGF-β1 is a multifunctional cytokine that is involved in multiple processes, such as inflammatory infiltration, cell proliferation, cell differentiation, and extracellular matrix deposition in tissue fibrosis, and can be activated by multiple mechanisms[17]. During fibrosis, it is derived mainly from macrophages, and its main effects are as follows: (1) TGF-β1 induces the activation of fibroblasts into Myofs and increases the expression of the Myof marker protein α-SMA[18]; and (2) It promotes the deposition of extracellular matrix and increases the synthesis of matrix components (Col I and Col III). S1P is an important lipid metabolite produced by the phosphorylation of sphingosine, which can act on intracellular targets or be exported outside the cell *via* related protein transporters and bind to a group of S1P receptors (S1PR, S1P1-5). This leads to the activation of different signaling pathways and subsequent cellular responses. Sphk1 is one of the key enzymes that catalyzes the phosphorylation of S1P. After activation, Sphk1 migrates from the cytoplasm to the cell membrane and catalyzes the phosphorylation of S1P in the catalytic component of the membrane[19]. TGF-β1 can significantly upregulate the gene and protein expression of Sphk1 in fibroblasts and promote fibrosis through the Sphk1/S1P pathway. Studies have confirmed that TGF-β1 affects the Sphk1-S1P signaling pathway to promote Myof activation in the intestine, liver, heart, lung, and other tissues. It also promotes α-SMA and collagen expression, resulting in fibrosis (Figure 2)[20,21]. For example, TGF-β1, a proven profibrotic factor in renal interstitial fibrosis, can inhibit the degradation

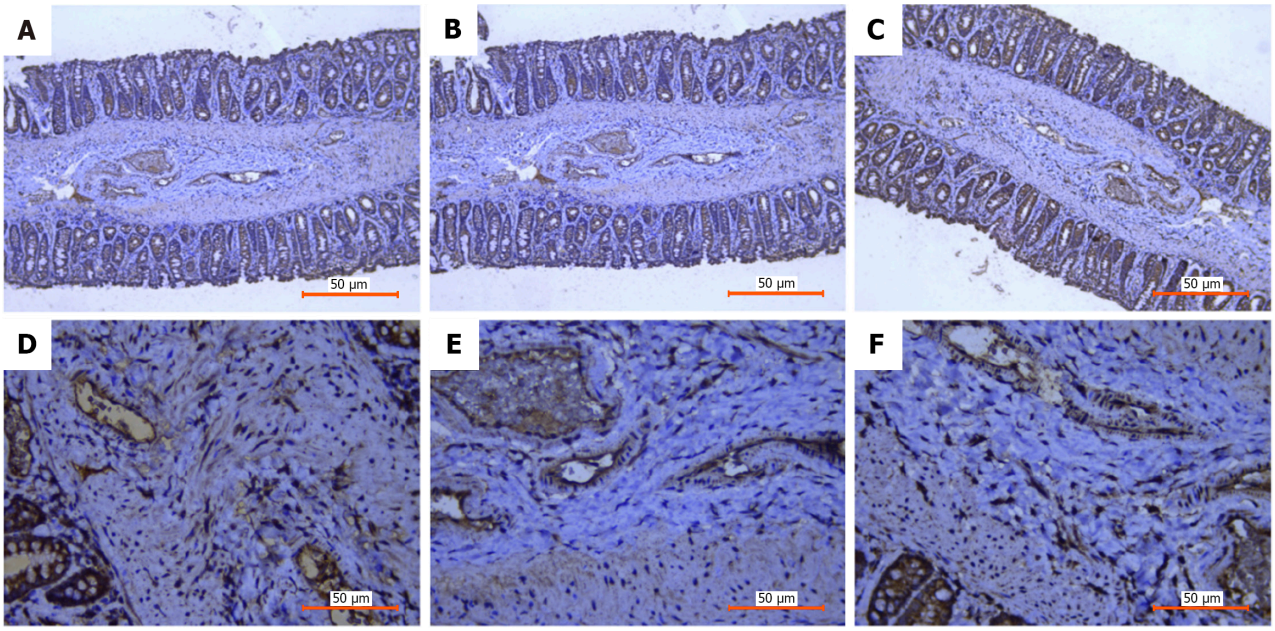


Figure 5 Immunohistochemical staining of internal hemorrhoid tissue. A: Sphingosine kinase 1 (100 ×); B: Sphingosine-1-phosphate receptor 1 (100 ×); C: Transforming growth factor-β1 (100 ×); D: Sphingosine kinase 1 (400 ×); E: Sphingosine-1-phosphate receptor 1 (400 ×); F: Transforming growth factor-β1 (400 ×).

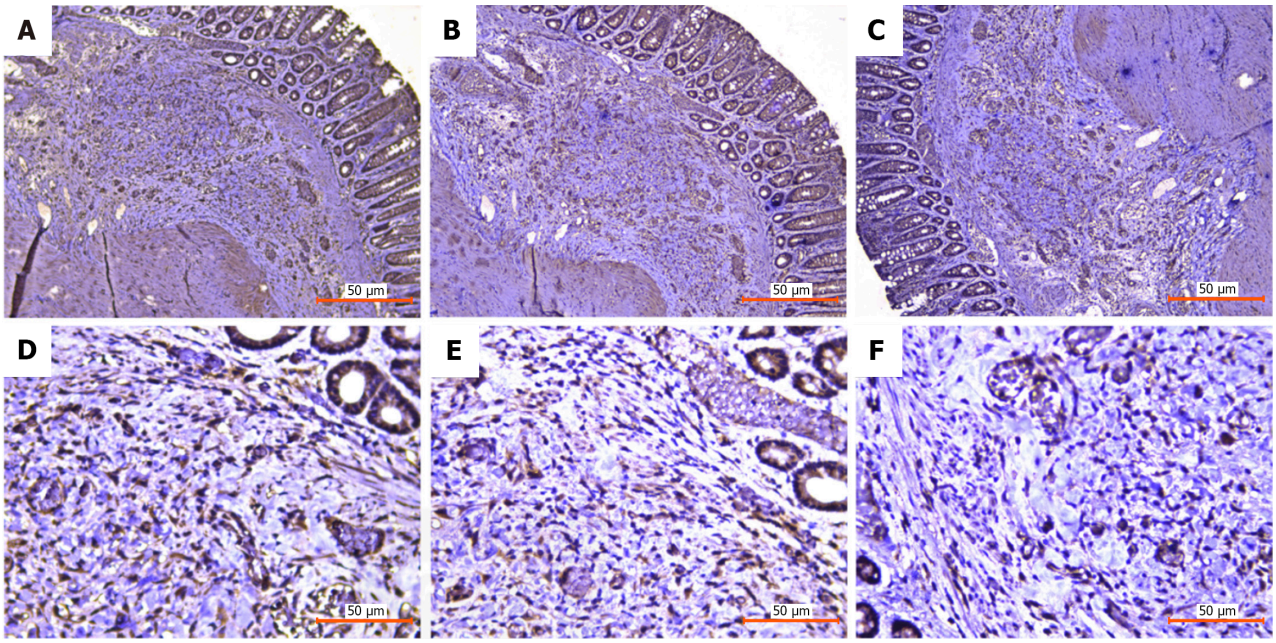


Figure 6 Immunohistochemical staining. A: Sphingosine kinase 1 (100 ×); B: Sphingosine-1-phosphate receptor 1 (100 ×); C: Transforming growth factor-β1 (100 ×); D: Sphingosine kinase 1 (400 ×); E: Sphingosine-1-phosphate receptor 1 (400 ×); F: Transforming growth factor-β1 (400 ×).

of the extracellular matrix and promote the production of collagen[22]. S1P is a bioactive sphingolipid metabolite that is produced by the phosphorylation of sphingosine by the highly conserved protein Sphk1, and the Sphk1/S1P signaling pathway can participate in the development of fibrosis and inflammation[23].

CONCLUSION

The spatial localization of key genes of the Sphk1-S1P and TGF-β1 pathways, *i.e.*, *Sphk1*, *S1PR1*, and *TGF-β1*, was compared (Figure 2E and Figure 3E). The expression levels of Sphk1-S1P and TGF-β1 pathway-related genes (Figure 2F and Figure 3F) were significantly increased in the area where fibroblasts were concentrated after Xiaozhiling injection. The above results reveal that fibroblasts and key genes of the Sphk1-S1P pathway are activated at the injection site.

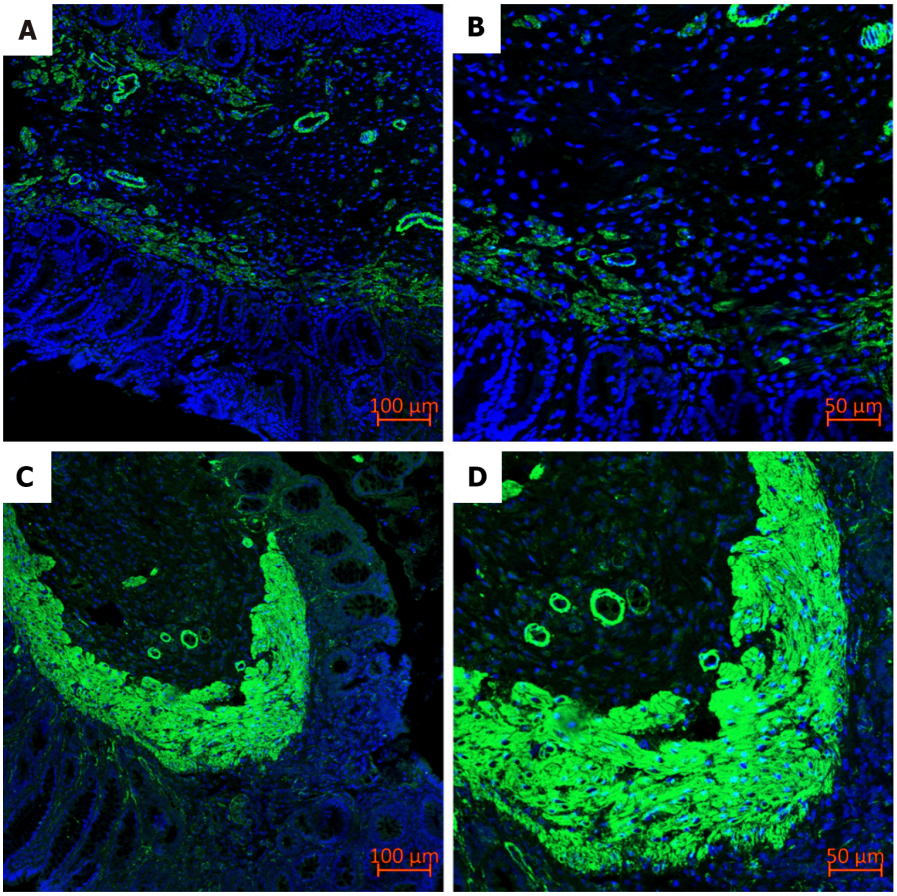


Figure 7 Immunofluorescence. A: Alpha-smooth muscle actin (α-SMA) in control group (100 ×); B: α-SMA in control group (200 ×); C: α-SMA in treatment group (100 ×); D: α-SMA in treatment group (200 ×).

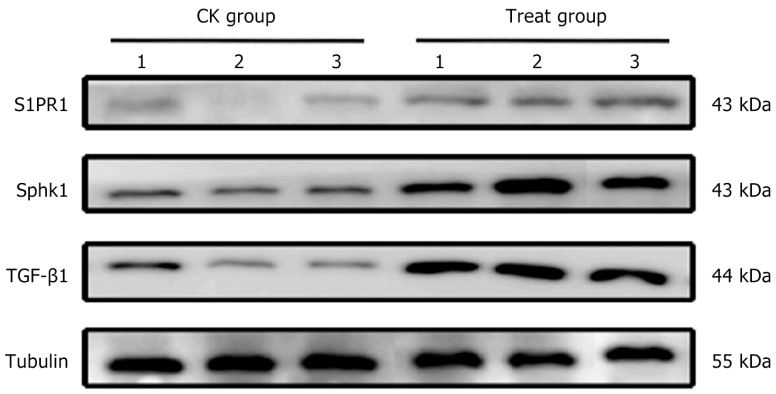


Figure 8 Expression of sphingosine kinase 1-sphingosine-1-phosphate pathway related proteins in rectal tissues. Sphk1: Sphingosine kinase 1; S1PR1: Sphingosine-1-phosphate receptor 1; TGF-β1: Transforming growth factor-β1.

Xiaozhiling was injected into the submucosa of the hemorrhoidal area, and through the upregulation of TGF-β1, a classic marker gene of the Sphk1-S1P signaling pathway, was specifically activated at the injection site, where it regulated MyoF activation. These findings suggest that, after Xiaozhiling injection, the Sphk1-S1P pathway can be activated to promote fibrosis.

FOOTNOTES

Author contributions: Ke MH contributed to research guidance, manuscript review, and financial support; Ke MH and Huang SY contributed to experiment design, article writing, and drawing, and they contributed equally to this article as co-first authors; Lin WG contributed to discussion of the article; Xu ZG contributed to the writing of the manuscript related to pathology; Zheng XX, Liu XB, Cheng YM, and Li ZF contributed to the performance of animal experiments; and all authors thoroughly reviewed and endorsed the

final manuscript.

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Institutional animal care and use committee statement: All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of Second People's Hospital Affiliated with Fujian University of Traditional Chinese Medicine, approval No. FJATCM-IAEC2018015.

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

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SYSTEMATIC REVIEWS

Association of *Clostridium difficile* infection with clinical outcomes of patients with inflammatory bowel disease: A meta-analysis

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Abstract

BACKGROUND

Clostridium difficile infection (CDI) is common in patients with inflammatory bowel disease (IBD).

AIM

To assess the association of CDI with clinical outcomes of IBD.

METHODS

PubMed, EMBASE, Web of Science, and the Cochrane Library databases were searched from inception to March 2024. Eligible articles included observational studies that reported on outcomes such as mortality, colectomy, hospitalization, intensive care unit (ICU) admission, complication rates, and length of hospital stay in IBD patients with and without CDI. Data were extracted, and a random-effects model was used to calculate pooled odds ratios (ORs) and mean differences (MDs).

RESULTS

As shown in the data from 21 studies with 1249158 participants, CDI significantly increased the risk of mortality in IBD patients [pooled OR = 4.569, 95% confidence intervals (95%CI): 2.584 to 8.079]. Although the pooled OR for colectomy was 1.409 (95%CI: 0.922 to 2.155), it was not statistically significant. Similarly, CDI did not impact hospitalization (pooled OR = 1.056, 95%CI: 0.512 to 2.179) and ICU admission outcomes (pooled OR = 1.970, 95%CI: 0.420 to 9.246) of patients with IBD. The rate of complications was comparable in the two groups (pooled OR =

0.658, 95%CI: 0.378 to 1.147). However, CDI was associated with a significantly more extended hospital stay (pooled MD = 0.349 days, 95%CI: 0.002 to 0.696).

CONCLUSION

CDI is linked to increased mortality and prolonged hospitalization in IBD patients. These results emphasize the need for early detection and appropriate management. Implementing routine CDI screening during IBD flare-ups and stringent infection control measures could mitigate severe complications and reduce the healthcare burden.

Key Words: *Clostridium difficile* infection; Inflammatory bowel disease; Mortality; Colectomy; Hospitalization; Meta-analysis

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Core Tip: *Clostridium difficile* infection (CDI) significantly complicates the management of patients with inflammatory bowel disease (IBD), exacerbating disease severity and leading to worse clinical outcomes. This systematic review and meta-analysis demonstrated the association of CDI with increased mortality and prolonged hospital stays in IBD patients. While CDI was not significantly linked to colectomy or other complications, its impact on healthcare resource utilization underscores the need for routine screening, timely treatment, and robust infection control measures. These findings provide critical insights into optimizing care strategies and reducing the burden of CDI in IBD management.

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INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory gastrointestinal condition[1] which significantly impacts the quality of life of patients and is associated with a substantial burden on the healthcare system[2].

Despite recent advances in disease management, IBD patients are still at increased risk for various complications, such as strictures, fistulas, and abscesses, which often require surgical intervention and increase morbidity and mortality[3,4]. Colectomy, a surgical procedure to remove part or all of the colon, is a common outcome for patients with severe or refractory IBD[5]. Additionally, these patients frequently require prolonged hospitalizations and experience adverse outcomes that further complicate disease management.

One of the significant infectious complications of IBD is *Clostridium difficile* infection (CDI)[6,7], a primary cause of healthcare-associated infections that is particularly prevalent in patients with compromised gut integrity. Research shows that CDI exacerbates the underlying IBD and leads to a more severe disease course[8], higher rates of morbidity, prolonged hospital stays, increased healthcare costs, and greater mortality[9]. Furthermore, exacerbation of IBD symptoms by CDI can also lead to more frequent and severe flare-ups, often resulting in increased rates of colectomy and other surgical interventions[10]. CDI can also complicate the medical management of patients with IBD, limiting therapeutic options and necessitating more aggressive treatment[6,7].

Despite the clear clinical implications, there is still no comprehensive evidence of the full spectrum of CDI-associated outcomes in IBD patients. Previous reviews have primarily focused on individual outcomes, such as colectomy rates[11-14]. However, the association of CDI with a broader range of critical outcomes, including mortality, overall complications, and hospitalization rates in IBD patients, is still unclear.

Nurses are crucial in managing IBD patients, particularly in monitoring symptoms, administering treatments, and providing patient education. Understanding the link between CDI and clinical outcomes of IBD will help nurses develop more effective care plans and improve patient outcomes. This study aimed to systematically evaluate the association of CDI with a wide array of clinical outcomes, including mortality, colectomy rates, complications, and hospitalization outcomes, in patients with IBD.

MATERIALS AND METHODS

Protocol registration

This study protocol was registered in PROSPERO (CRD42024547255).

Eligibility criteria

The review included studies assessing the association of CDI with outcomes in patients with IBD. The inclusion criteria

were as follows: (1) Studies of adult IBD patients (aged 18 years and older), including both CD and UC cases; (2) Studies reporting the association of CDI with clinical outcomes such as mortality, colectomy rates, complications (defined as clinical events related to IBD or its treatment, including bowel obstruction, strictures, fistula, abscess formation, or infections such as sepsis and toxic megacolon), and hospitalization outcomes; (3) Studies providing clear data on the presence and absence of CDI in IBD patients; and (4) Cohort, cross-sectional, and case-control peer-reviewed studies.

The exclusion criteria were as follows: (1) Studies not reporting relevant outcomes specific to CDI in IBD patients; (2) Studies in pediatric populations (younger than 18 years); (3) Case reports, case series, editorials, commentaries, or not peer-reviewed studies; (4) Abstracts or conference presentations.

Information sources

A systematic search was conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov), EMBASE (https://www.embase.com), Web of Science (https://www.webofscience.com), and the Cochrane Library (https://www.cochranelibrary.com) for studies from inception until March 2024. Additionally, bibliography sections of identified studies were manually searched. The final literature search was performed on May 31, 2024.

Search strategy

The search strategy used free text words and Medical Subject Headings terms. The search terms used included "inflammatory bowel disease", "colitis, ulcerative", "Crohn's disease", "inflammatory bowel", "IBD", "ulcerative colitis", "Crohn's", "*Clostridium difficile*", and "*C. difficile*". Boolean operators (AND/OR) were used to refine search results. Reference sections of recent reviews and publications from major gastroenterology conferences were also screened. Additionally, authors of identified studies were contacted for further data or clarification of study methodologies when necessary. A detailed search strategy for different databases is shown in Supplementary material.

Study selection

Two independent reviewers assessed the titles and abstracts of identified papers and reviewed full texts of potentially relevant studies. Any discrepancies regarding study eligibility were resolved by consensus or consulting with a third senior reviewer. Rayyan software was used to identify and remove duplicate reports while maintaining a clear and auditable trail of the review process[15].

Data collection

Data were independently extracted by two reviewers using a standardized form designed for this study and pre-tested on a subset of studies to ensure its effectiveness in capturing all pertinent data points clearly and concisely. The data collected included study characteristics, patient characteristics, method of CDI diagnosis, and outcome assessment. The reviewers cross-checked each other's data entries to correct discrepancies and confirm data integrity. In cases where data were unclear or missing, study authors were contacted to provide further details or clarification to ensure the completeness and accuracy of the data set.

Study data and outcomes

The primary outcomes of interest were mortality, colectomy rates, complications, and hospitalization outcomes in patients with IBD who also had CDI. Mortality was defined as death occurring within specified follow-up periods, including in-hospital mortality and long-term mortality. Colectomy rates referred to the percentage of patients undergoing surgical removal of part or all of the colon. Complications included any reported adverse events such as bowel obstruction, strictures, fistula, or infection. Hospitalization outcomes included the length of hospital stay, readmission rates, and the need for intensive care. Data for all measures, time points, and analyses provided in the studies were collected. In cases where multiple time points or analyses were reported, priority was given to the most clinically relevant and commonly reported time points, such as immediate postoperative outcomes and follow-ups at one year.

In addition to the primary outcomes, data on various other variables was collected to provide a comprehensive understanding of the study populations and methodologies. These included: (1) Patient characteristics such as age, gender, IBD type (UC or CD), hospitalization status (inpatient or outpatient), and comorbidity scores; (2) Study characteristics, including the primary author, year of publication, time period of the study, geographic location, study design (cohort, cross-sectional, or case-control), and whether the study was published as a full paper or abstract; (3) Details of CDI diagnosis methods (*e.g.*, enzyme-linked immunosorbent assay, enzyme immunoassay, cytotoxicity assay, and stool polymerase chain reaction); (4) Intervention characteristics, which provided specific details of treatments and interventions used for managing IBD and CDI; and (5) Information regarding funding sources and potential conflicts of interest (to account for the influence of financial biases on study outcomes).

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS)[16] was used to assess the risk of bias. The NOS evaluates studies based on three key domains: Selection of study groups (maximum of 4 points), comparability of groups (maximum of 2 points), and ascertainment of the exposure or outcome of interest for case-control or cohort studies, respectively (maximum of 3 points). Each study was carefully rated on these domains, with a maximum possible score of 9 points. Studies scoring 7-9 were categorized as having low risk of bias, 5–6 as having moderate risk, and below 5 as having high risk of bias.

Two independent reviewers conducted the evaluations to ensure a rigorous and reliable assessment process. Pre-specified guidelines were used to assign scores for each domain, ensuring consistency in applying NOS criteria across studies. Any disagreements between reviewers were documented and discussed in detail. A third senior reviewer was consulted to resolve the discord if a consensus could not be reached. This triangulated approach ensured objectivity and minimized the potential for bias during the quality assessment process.

Statistical analysis

Effect measures used in this meta-analysis included odds ratios (ORs) with 95% confidence intervals (95%CIs) for dichotomous outcomes, such as mortality, and mean differences (MDs) for continuous outcomes, such as the length of hospital stay. Studies were tabulated based on intervention characteristics to determine eligibility for synthesis and compared against predefined criteria. Data preparation involved addressing missing summary statistics and converting data to ensure consistency. Results from individual studies and syntheses were tabulated and visually displayed using forest plots. A random-effects model was employed to synthesize results due to anticipated heterogeneity, assessed by the I^2 statistic. Meta-analyses were conducted using Stata version 17[17]. The funnel plot was used for publication bias assessment. Sensitivity analysis by excluding studies, one at a time, was done to identify any potential outliers or influential studies that could disproportionately affect the meta-analysis. Meta-regression was performed to explore the sources of heterogeneity for outcomes with at least 10 studies. The factors assessed for meta-regression were the sample size, year of publication, age, gender distribution, IBD duration, and behavioral habits like smoking and alcohol use. A P value less than 0.05 indicates that the factor significantly contribute to the heterogeneity and adjusted R-squared value was used to explain the extent of heterogeneity explained by the factor.

RESULTS

Study screening and selection

The initial pool of studies contained 1652 records that were retrieved from PubMed (n = 204), Embase (n = 834), Web of Science (n = 452), and Cochrane Central (n = 162) databases. Following an auto-deduplication process, 388 records were removed, and further 19 duplicates were removed manually. Of the remaining 1245 records subjected to the primary title and abstract screening, 1181 were excluded. Subsequently, 64 reports were assessed for eligibility. Of them, 44 were eliminated. The reasons for elimination were as follows: 32 studies assessed only risk factors, 9 did not report relevant outcomes, and 2 were excluded for other reasons. Ultimately, 21 papers were included in the analysis (Figure 1)[18-38].

Characteristics of included studies

This review encompassed a diverse range of study designs and geographic locations (Table 1). The studies were published between 2009 and 2023 in the United States, China, Canada, Saudi Arabia, Brazil, South Korea, and Israel. The sample sizes of the studies varied significantly, ranging from 66 to 562000 participants. The number of CDI-positive cases ranged from 8 to 3832 across the studies, and the median age of the cohort ranged from 24 [interquartile range (IQR): 19-33] to 49 (IQR: 34-62) years. The percentage of male patients ranged from 36.3% to 77.1%.

The studies included both CD and UC patients, with 100% of the studies focusing on both conditions simultaneously. Smoking and alcohol use were also documented, although not consistently across all studies. According to studies that reported on the specific segments of the gastrointestinal tract affected, the location of IBD involvement varied. The prevalence of colon-dominant disease ranged from 10% to 55%, and that of ileum-dominant disease from 26.5% to 55%. The severity of IBD was reported in terms of remission, mild, moderate, and severe cases, with some studies providing detailed percentages for each category, with the reported remission rates of 47.9%, mild IBD rates of 50%, moderate IBD rates of 47.3%, and severe IBD rates of 39.2%.

Mortality

The meta-analysis of mortality outcomes included data from ten studies (Figure 2A). The pooled OR for mortality of patients with IBD and CDI was 4.569 (95%CI: 2.584 to 8.079), indicating a significantly increased risk of mortality in this patient population compared to patients without CDI, with substantial heterogeneity (I^2 = 91.19%). The Egger test for small-study effects yielded a beta coefficient of -0.75 [standard error (SE): 0.570, P = 0.1879], indicating no significant evidence of publication bias (Supplementary Figure 1A). Meta-regression showed that the sample size was the only significant factor, explaining 90.15% of the total heterogeneity. Although the association of other factors with mortality was non-significant, IBD duration could explain 53.92% of heterogeneity and the year of publication 17.7% of heterogeneity. Sensitivity analysis revealed that the effect sizes did not differ significantly in magnitude/direction after excluding any single study.

Colectomy

The meta-analysis that examined the need for colectomy included 17 studies, with a pooled OR of 1.409 (95%CI: 0.922 to 2.155; Figure 2B). These results indicated a slightly but not significantly elevated risk of requiring colectomy in IBD patients with CDI compared to patients without, with substantial heterogeneity (I^2 = 84.44%). The Egger test for small-study effects showed a beta coefficient of -0.74 (SE: 0.802, P = 0.3551), indicating no significant publication bias (Supplementary Figure 1B). Meta-regression results indicated that none of the factors showed a significant contribution to the heterogeneity. However, the sample size explained 20.4%, and gender distribution explained 21.5% of the total

Table 1 Characteristics of included studies

Ref.	Country	Study design	Sample size	CDI positive cases	CDI negative cases	Age (mean, SD; median, IQR; range), years	Gender (% male)	IBD type	IBD duration (years)	Smoking (% of current smokers)	Location of IBD	IBD severity (remission, mild, moderate, severe)	Co-morbidities	Risk of bias assessment (NOS score)
AlKhormi *et al* [18], 2023	Saudi Arabia	Case-control study	95	16	79	Median: 24 (19-33)	47.4	Both CD and UC	6	11.7	Colon-dominant CD-10, ileum-dominant CD-55, CD unclassified-3	-	Diabetes: 9.4, hypertension: 8.3	5
Chen *et al*[19], 2019	China	Prospective observational cohort study	230	32	198	Mean: 37.7 (14.3)	66.5	Both CD and UC	-	-	-	Remission: 3.9, mild: 34.3, moderate: 47.3, severe: 14.3	-	5
Garcia *et al* [20], 2018	Brazil	Prospective cohort study	66	19	47	Mean: 40.95 (13.2)	36.3	Both CD and UC	6	9.1	Extensive-36.8, left-sided UC-21.1, colonic/ileocolonic CD-42.1	Mild-to-moderate: 84.2, severe: 15.8	-	7
Gros *et al*[21], 2023	Spain	Retrospective case-control study	105	35	70	Median: 48 (28-65)	77.1	Both CD and UC	-	11.4	-	-	Diabetes: 6.6	7
Joshi *et al*[22], 2017	United Kingdom	Retrospective cohort study	94	47	47	-	-	Both CD and UC	-	-	-	-	-	7
Kariv *et al*[23], 2011	United States	Retrospective case-control study	78	39	39	Median: 39 (33–55)		UC	7.6	30.7	-	-	Diabetes: 5.12; other comorbidities: 27.8	5
Kim *et al*[24], 2018	Korea	Prospective multicentre observational study	81	8	73	Mean: 39.6 (14.5)	49.3	UC	3.4	-	-	-	-	3
Li *et al*[25], 2018	China	Case-control retrospective study	197	60	137	Median: 38.0 (28.0-49.0)	60.9	Both CD and UC	12	16.2	Proctitis-1, left-sided colitis-24.5, extensive colitis-74.5	Mild: 16.7, moderate: 44.1, severe: 39.2	Diabetes: 6.6	7
Maharshak *et al*[26], 2018	Israel	Retrospective case-control study	383	28	355	Median: 38.1 (30-60)	42.8	Both CD and UC	6	20.1	Small intestine-11.8, colon-29.4, ileocolonic-58.8	-	Charlson comorbidity index ≥ 2 = 35.7%	5
Samman *et al* [27], 2023	Saudi Arabia	Retrospective cohort study	602	53	549	Mean: 36.58 (14.03)	48.8	Both CD and UC	-	2.4	-	-	-	7

Xu *et al*[28], 2019	China	Retrospective cohort study	102	34	68	Median: 44.5 (29.0-60.0)	47.1	Both CD and UC		12.7	-	Remission: 16.2, mild: 45.1, moderate: 38.2	Diabetes: 9.5	5
Gu *et al*[35], 2017	China	Retrospective cohort study	260	13	247	Mean: 35.7 (16.2)	56.1	Both CD and UC	-	-	Ileum-34.6, colon-38.8, ileocolon-26.5, upper GI involvement-1.92	Remission: 15.7, mild: 50, moderate: 34.3	-	3
Zhang *et al* [29], 2016	China	Retrospective cohort study	646	99	547	Median: 33 (16-76)	63.7	Both CD and UC	-	-	-	Remission: 47.9, mild: 36.2, severe: 15.7	-	5
Bernard *et al* [30], 2022	United States	Retrospective cohort study	300	161	139	Median: 49 (34–62)	47.7	Both CD and UC	9.8	16.6	-	-	-	7
Negrón *et al* [31], 2016	Canada	Cohort study	1754	81	1673	Median: 41	50.4	Both CD and UC	-	-	-	-	-	7
Rezapour *et al* [32], 2018	United States	Retrospective cohort study	224500	3832	220668	Mean: 45 (20.7)	47	Both CD and UC	-	-	-	-	-	5
Saffouri *et al* [33], 2017	United States	Prospective cohort study	562000	20798	541202		47.1	Both CD and UC	-	-	-	-	-	5
Anderson *et al* [34], 2017	United States	Propensity scores matched analysis	198	66	192	Mean: 45.4 (15.2)	43.7	Both CD and UC	-	-	Ileal-26.5, colonic-31.6, ileocolonic-44.9, upper GI-4.1	-	-	5
Navaneethan *et al*[36], 2012	United States	Prospective cohort study	146	45	101	Mean: 45.9 (17.2)	65	Both CD and UC	2.3	-	Rectum-4, left sided-11.5, extensive-84.4	-	-	5
Murthy *et al* [37], 2012	Canada	Retrospective cohort study		181	1835		47	UC	2	-	-	-	-	7
Jodorkovsky *et al*[38], 2010	United States	Prospective cohort study	99	47	52		52.4	UC	-	-	-	-	-	5

CDI: *Clostridium difficile* infection; IQR: Interquartile range; CD: Crohn's disease; GI: Gastrointestinal; IBD: Inflammatory bowel disease; NOS: Newcastle Ottawa Scale; UC: Ulcerative colitis.

heterogeneity. Sensitivity analysis revealed that the effect sizes did not differ significantly in magnitude/direction after excluding any single study.

Hospitalization

Nine studies reported hospitalization outcomes (Figure 2C). CDI had no significant association with hospitalization risks, with a pooled OR of 1.056 (95%CI: 0.512 to 2.179) and substantial heterogeneity (I^2 = 82.21%). The Egger test for small-study effects showed a beta coefficient of 0.88 (SE: 1.312, P = 0.5014), indicating no significant evidence of publication bias (Supplementary Figure 1C). Sensitivity analysis revealed that the effect sizes did not differ significantly in terms of magnitude/direction after excluding any single study.

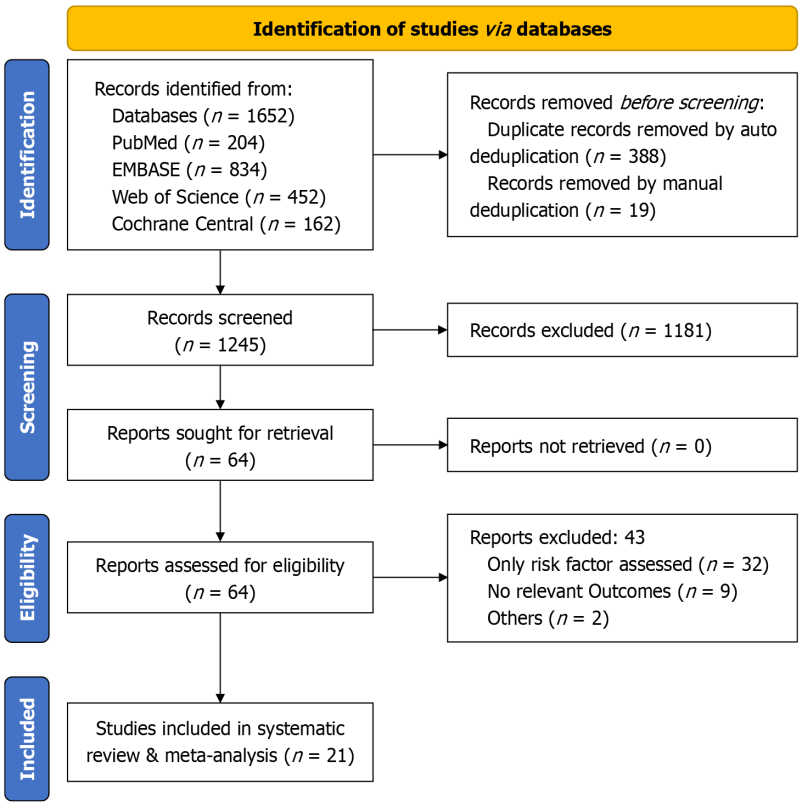


Figure 1 PRISMA flowchart showing the study selection process.

ICU admission

The meta-analysis that examined ICU admission outcomes included four studies, with a pooled OR of 1.970 (95%CI: 0.420 to 9.246), which indicated no significant difference in the risk of ICU admission in patients with or without CDI (Figure 2D). The Egger test for small-study effects showed a beta coefficient of -0.63 (SE: 1.764, P = 0.7197), indicating no significant evidence of publication bias. Sensitivity analysis revealed that the effect sizes did not differ significantly in terms of magnitude/direction after excluding any single study.

Complications

The meta-analysis on complication rates incorporated data from three studies (Figure 2E). The pooled OR for complications in patients with IBD and CDI was 0.658 (95%CI: 0.378 to 1.147), suggesting a comparable incidence of complications in the two groups. The Egger test for small-study effects yielded a beta coefficient of 1.67 (SE: 5.161, P = 0.7462), indicating the lack of publication bias. Sensitivity analysis revealed that the effect sizes did not differ significantly in terms of magnitude/direction after excluding any single study.

Mean duration of hospitalization

The meta-analysis that evaluated the mean duration of hospitalization included data from eight studies, with a pooled MD of 0.349 days (95%CI: 0.002 to 0.696; Figure 2F). The result showed that CDI was associated with considerably longer hospital stays in IBD patients. The included studies had extremely high heterogeneity (I^2 of 99.53%). The Egger test for small-study effects revealed a beta coefficient of -2.34 (SE: 1.485, P = 0.1156), indicating no significant evidence of publication bias (Supplementary Figure 1D). Sensitivity analysis revealed that the effect sizes did not differ significantly in terms of magnitude/direction after excluding any single study.

DISCUSSION

Our study demonstrated a link between CDI and significantly increased mortality and extended hospital stays in IBD patients.

The study showed that CDI positivity in patients with IBD was associated with significantly increased mortality, with a pooled OR of 4.569 (95%CI: 2.584 to 8.079). This finding confirms the results reported by Tariq *et al*[13] in 2019, who also observed a heightened mortality risk among IBD patients with CDI (OR = 4.39; 95%CI: 3.56-5.42), particularly in those with UC. The increased mortality risk is attributed to the severe complications associated with CDI, such as toxic megacolon, sepsis, and multi-organ failure[39]. In IBD patients, the compromised intestinal mucosal barrier and the use of immunosuppressive therapies exacerbate these complications, leading to worse clinical outcomes and increased

A

Study	C. difficile + Died	C. difficile + Survived	C. difficile - Died	C. difficile - Survived	Odds ratio With 95%CI	Weight (%)
Gros 2022	3	32	4	66	1.55 [0.33, 7.33]	8.27
Joshi 2016	2	45	0	47	5.22 [0.24, 111.71]	2.98
Maharshak 2018	4	24	7	348	8.29 [2.27, 30.29]	10.18
YuBeiGu 2017	0	13	1	246	6.09 [0.24, 156.53]	2.69
Bernard 2022	2	159	2	137	0.86 [0.12, 6.20]	6.01
Rezapour 2018	137	3694	1501	219167	5.42 [4.53, 6.47]	21.06
Saffouri 2017	1269	19529	3788	537413	9.22 [8.64, 9.84]	21.44
Abdersonet 2017	6	60	12	180	1.50 [0.54, 4.17]	12.71
Murthy 2012	6	174	7	1828	9.00 [2.99, 27.09]	11.93
Jodorkovsky 2009	1	46	0	52	3.39 [0.13, 85.19]	2.73
Overall					4.57 [2.58, 8.08]	

Heterogeneity: $T^2 = 0.39$, $I^2 = 91.19\%$, $H^2 = 11.35$
Test of $\theta_i = \theta_j$: Q(9) = 51.88, $P = 0.00$
Test of $\theta = 0$: Z = 5.22, $P = 0.00$



Random-effects REML model

B

Study	C. difficile + Colectomy +	C. difficile + Colecomy -	C. difficile - Colectomy +	C. difficile - Colectomy -	Odds ratio With 95%CI	Weight (%)
Alkhormi 2023	2	14	34	45	0.19 [0.04, 0.89]	4.13
Chen 2019	10	22	14	184	5.97 [2.37, 15.05]	6.37
Gros 2022	10	25	15	55	1.47 [0.58, 3.71]	6.35
Joshi 2016	1	46	4	43	0.23 [0.03, 2.17]	2.60
Kariv 2010	12	27	13	26	0.89 [0.34, 2.30]	6.26
Kim 2018	0	8	2	71	1.68 [0.07, 38.04]	1.54
Li 2018	12	22	15	53	1.93 [0.78, 4.78]	6.44
Maharshak 2018	5	21	49	306	1.49 [0.54, 4.13]	5.98
Xu 2019	9	25	11	57	1.87 [0.69, 5.06]	6.07
YuBeiGu 2017	1	12	19	228	1.00 [0.12, 8.11]	2.84
Zhang 2016	25	74	90	457	1.72 [1.03, 2.85]	8.08
Bernard 2022	3	158	8	131	0.31 [0.08, 1.20]	4.76
Negron 2016	24	57	210	1463	2.93 [1.78, 4.83]	8.11
Saffouri 2017	936	19862	42754	498447	0.55 [0.51, 0.59]	9.11
Navaneethan 2012	16	29	10	91	5.02 [2.05, 12.27]	6.50
Murthy 2012	22	159	180	1655	1.27 [0.79, 2.04]	8.20
Jodorkovsky 2009	21	25	13	39	2.52 [1.07, 5.92]	6.66
Overall					1.41 [0.92, 2.16]	

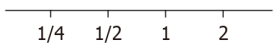
Heterogeneity: $T^2 = 0.51$, $I^2 = 84.44\%$, $H^2 = 6.43$
Test of $\theta_i = \theta_j$: Q(16) = 150.82, $P = 0.00$
Test of $\theta = 0$: Z = 1.58, $P = 0.11$



C

Study	C. difficile + Complications +	C. difficile + Complications -	C. difficile - Complications +	C. difficile - Complications -	Odds ratio With 95%CI	Weight (%)
Chen 2019	8	5	82	58	1.13 [0.35, 3.63]	22.63
Gros 2022	6	29	24	46	0.40 [0.14, 1.09]	30.32
YuBeiGu 2017	13	13	145	102	0.70 [0.31, 1.58]	47.04
Overall					0.66 [0.38, 1.15]	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: Q(2) = 1.83, $P = 0.40$
Test of $\theta = 0$: Z = -1.48, $P = 0.14$



Random-effects REML model

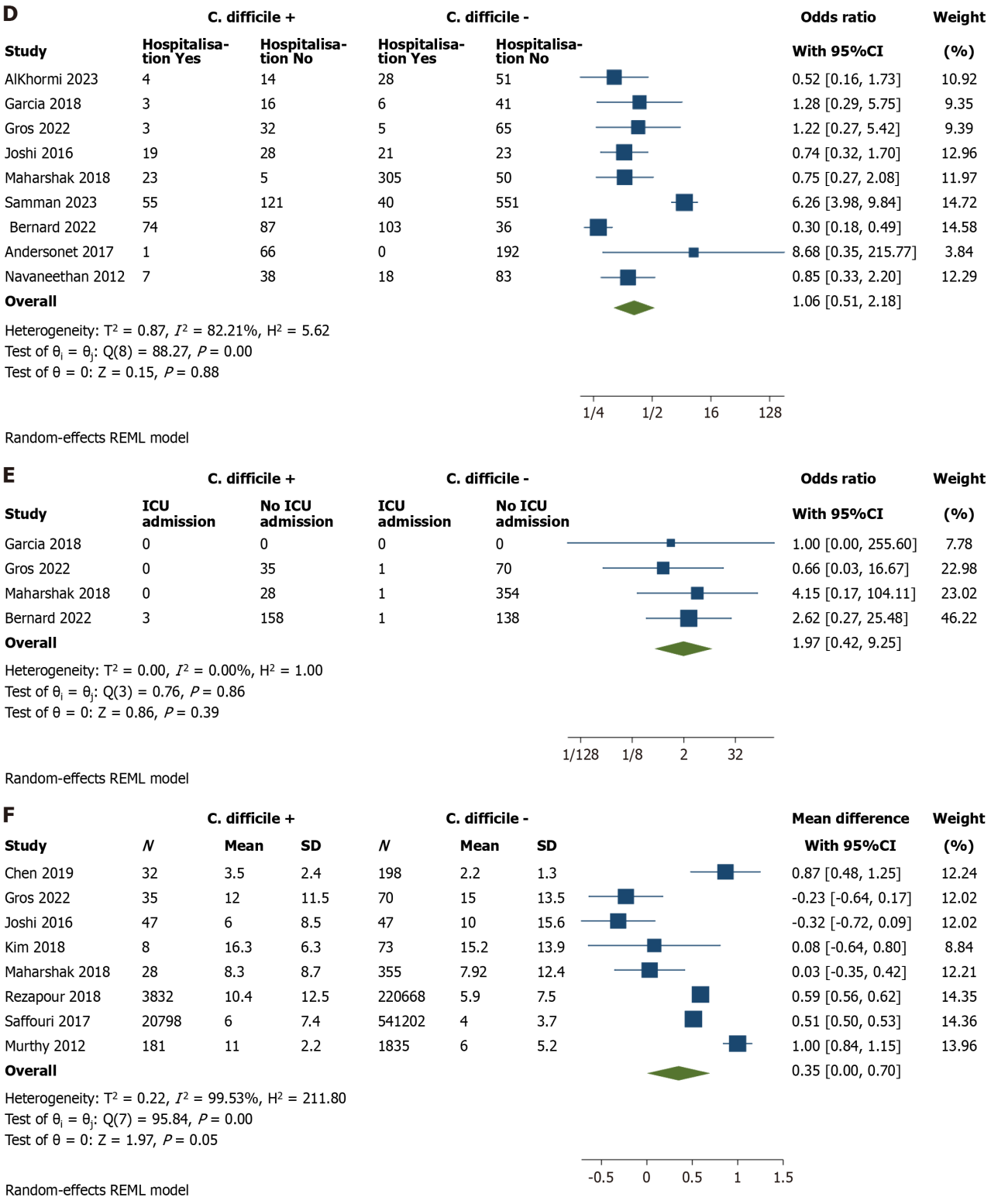


Figure 2 Forest plots showing association between *Clostridium difficile* infection and outcomes. A: Mortality; B: Colectomy rate; C: Complications; D: Hospitalization; E: Intensive care unit admission; F: Duration of hospital stay.

mortality[40]. Our study found a somewhat higher risk of needing colectomy in IBD patients with CDI, with a pooled OR of 1.409 (95%CI: 0.922 to 2.155). However, the lack of statistical significance suggests a potential but inconclusive association. This contrasts with the finding from Chen *et al*[11] in 2017, who reported a significant increase in colectomy risk (OR = 1.90; 95%CI: 1.23-2.93) among UC patients with CDI. The discrepancy might be due to different study populations or diagnostic criteria for CDI, or variations in medical and surgical management across studies. Additionally, it is plausible that the presence of CDI further exacerbates colonic inflammation and damage, which can lead to treatment-refractory disease and the subsequent need for surgical intervention.

Our study found no significant difference in hospitalization rates between IBD patients with and without CDI, with a pooled OR of 1.056 (95%CI: 0.512 to 2.179). This finding aligns with a study by Law *et al*[12] in 2017, who also reported no significant increase in short-term hospitalization rates in patients with CDI (OR = 1.35; 95%CI: 0.68-2.67). While the immediate hospitalization rates may not differ significantly, the prolonged duration of hospital stays in CDI patients, as evidenced by our pooled MD of 0.349 days (95%CI: 0.002 to 0.696), underscores the substantial healthcare burden and increased resource use associated with managing CDI in IBD patients. Such prolonged hospitalization can be attributed to the need for more intensive medical management and monitoring of CDI complications.

Our study reported comparable rates of ICU admission and complications in IBD patients with and without CD [a pooled OR of 1.970 (95%CI: 0.420 to 9.246) and 0.658 (95%CI: 0.378 to 1.147), respectively]. These results are in line with the findings of Law *et al*[12] in 2017. The lack of significant differences may suggest that while CDI contributes to prolonged hospital stays, it does not necessarily increase the immediate severity of the disease to the extent that it would require ICU care or lead to additional complications. Early detection and effective management of CDI, therefore, may mitigate the need for more extensive care levels despite the overall increased burden of the disease.

Research shows that CDI exacerbates IBD outcomes through a combination of toxin-mediated and immune response mechanisms. CDI toxins A and B cause direct cytotoxic effects on colonic epithelial cells, disrupting the mucosal barrier and inducing inflammation[41]. This disruption worsens the underlying pathology of IBD, characterized by a compromised intestinal barrier and dysregulated immune response[42]. The inflammatory cascade triggered by CDI toxins includes upregulation of pro-inflammatory cytokines (IL-1β, IL-6, and tumor necrosis factor-alpha) that may further aggravate mucosal inflammation and damage. Patients with IBD, who often undergo immunosuppressive therapies, have weakened immunity and ability to combat the infection, leading to a prolonged and more severe course of the disease[43]. These mechanisms have profound clinical significance, as they further emphasize the need for aggressive and timely management of CDI in IBD patients. Early intervention with appropriate antibiotics, consideration of immunomodulatory therapy adjustments, and close monitoring for complications are all essential strategies to mitigate the adverse impacts of CDI on this vulnerable population. Nurses are pivotal in implementing these strategies, as they are often the first to detect early signs of CDI in IBD patients and initiate timely interventions. They can significantly reduce the risk of severe outcomes by conducting routine assessments, educating patients on recognizing symptoms, and ensuring their adherence to treatment plans. Furthermore, nursing interventions focused on infection control practices and patient education play a crucial role in minimizing the transmission of CDI within healthcare settings.

This study has several strengths, including a comprehensive systematic review and meta-analysis that integrates data from a diverse range of studies, enhancing the generalizability of our findings. The use of rigorous inclusion criteria and standardized methods for data extraction and analysis ensures the reliability and validity of the results. Additionally, a large, pooled sample size provides robust statistical power to detect significant associations.

However, our study has limitations. The detected heterogeneity in study design, population characteristics, and diagnostic criteria for CDI may have affected the consistency of the findings. Furthermore, the reliance on observational studies may have introduced bias, as some confounding factors were not adequately controlled for in the primary studies. We could not perform subgroup analyses comparing outcomes between UC and CD due to the lack of stratified data in the included studies. Lastly, despite efforts to include unpublished data and grey literature, the potential for publication bias cannot be entirely ruled out. Therefore, our results and their implications for clinical practice must be considered cautiously.

Early detection and timely management are vital for improving outcomes in IBD patients with CDI. Delayed therapy has been shown to result in worsened outcomes, emphasizing the importance of implementing specific strategies to address this issue. For instance, the routine administration of stool testing for *Clostridium difficile* toxins or PCR-based diagnostic tests should be integrated into standard care protocols for IBD patients, particularly during flare-ups or hospital admissions. Early identification can enable the prompt initiation of evidence-based treatments, such as oral vancomycin or fidaxomicin, which have demonstrated superior efficacy in reducing morbidity and mortality in CDI patients. Additionally, stringent infection control measures, including isolation of infected patients, hand hygiene adherence, and environmental disinfection, are critical to limiting the spread of CDI, especially in immunocompromised IBD populations. Incorporating antimicrobial stewardship programs can further optimize the use of antibiotics, reducing the risk of recurrent CDI and minimizing complications.

Our findings suggest that routine CDI screening protocols should be systematically implemented during IBD exacerbations or before initiating immunosuppressive therapies, given the elevated risk of CDI in these scenarios. For instance, targeted screening during hospital admissions or in cases of symptoms such as diarrhea and abdominal pain can facilitate early diagnosis and mitigate severe outcomes. Furthermore, a multidisciplinary approach involving gastroenterologists, infectious disease specialists, and clinical pharmacists is essential to developing personalized management plans that address the unique challenges of CDI in IBD patients. These recommendations underscore the need for proactive and integrated clinical strategies to reduce CDI-related mortality, complications, and healthcare burden. By emphasizing early detection, effective antimicrobial therapy, and robust infection control measures, clinicians can significantly improve outcomes and quality of care for this vulnerable patient population.

Future research should focus on exploring the differential impact of CDI on CD and UC through well-designed, stratified studies. Longitudinal research is needed to evaluate the effectiveness of routine CDI screening and antimicrobial stewardship programs in improving outcomes in IBD patients. Additionally, studies assessing patient-centered outcomes, such as quality of life and healthcare costs, can provide a more comprehensive understanding of the burden of CDI in IBD.

CONCLUSION

This study emphasizes the significant association of CDI with mortality in patients with IBD, underscoring the critical need for early detection and targeted treatment. While the association between CDI and colectomy or hospitalization was less conclusive, the extended hospital stays observed in CDI patients are indicative of the increased healthcare burden. The results also underscore the importance of preventive measures, including judicious antibiotic use and infection control practices. Implementing routine CDI screening and prompt management in IBD care can improve patient outcomes and reduce complications.

FOOTNOTES

Author contributions: Qi HX conceived and designed the study; Qi HX, Wang Q, and Zhou GQ collected the data and performed the analysis; Qi HX was involved in the writing of the manuscript and is responsible for the integrity of the study; all authors have read and approved the final manuscript.

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SYSTEMATIC REVIEWS

Perforated peptic ulcer in pregnancy and puerperium: A systematic review

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Abstract

BACKGROUND

Peptic ulcer disease (PUD) during pregnancy is extremely rare. Perforated peptic ulcer (PPU) during pregnancy has high maternal and fetal mortality. Symptoms attributed to pregnancy and other diagnoses make the diagnosis of preoperative PPU during pregnancy and puerperium challenging.

AIM

To identify predictive factors for early diagnosis and treatment, and the association between the diagnosis and maternal/neonatal outcomes.

METHODS

We searched PubMed, PubMed Central, and Google Scholar. Articles were analyzed following preferred reporting items for systematic reviews and meta-analysis. The search items included: 'ulcer', 'PUD', 'pregnancy', 'puerperium', 'postpartum', 'gravid', 'labor', 'perforated ulcer', 'stomach ulcer', 'duodenal ulcer', 'peptic ulcer'. Additional studies were extracted by reviewing reference lists of retrieved studies. We included all available full-text cases and case series. Demographic, clinical, obstetric, diagnostic and treatment parameters, and outcomes were collected.

RESULTS

Forty-three cases were collected. The mean maternal age was 30.9 years; 36.6% were multiparous, and 63.4% were nulliparous or primiparous, with multiparas being older than primiparas. Peptic ulcer perforated in 44.2% of postpartum and 55.8% of antepartum patients. Antepartum PPU incidence increased with advancing gestation 2.3% in the first, 7% in the second, and 46.5% in the third

trimester. The most common clinical findings were abdominal tenderness (72.1%), rigidity (34.9%), and distension (48.8%). Duodenal ulcer predominated (76.7%). In 79.5%, the time from delivery to surgery or vice versa was > 24 hours. The maternal mortality during the third trimester and postpartum was 10% and 31.6%, respectively. The trimester of presentation did not influence maternal mortality. The fetal mortality was 34.8%, with all deaths in gestational weeks 24-32.

CONCLUSION

Almost all patients with PPU in pregnancy or puerperium presented during the third trimester or the first 8 days postpartum. Early intervention reduced fetal mortality but without influence on maternal mortality. Maternal mortality did not depend on the use of X-ray imaging, perforation location, delivery type, trimester of presentation, and maternal age. Explorative laparoscopy was never performed during pregnancy, only postpartum.

Key Words: Peptic ulcer disease; Perforated peptic ulcer; Pregnancy; Puerperium; Outcomes; Systematic review

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Core Tip: The correct diagnosis of perforated peptic ulcer in pregnancy was frequently delayed. Almost all patients presented during the third trimester or the first 8 days postpartum. Antepartum incidence increased as the pregnancy advanced. Common symptoms were abdominal tenderness and distension. Early imaging, including plain abdominal X-ray and abdominal ultrasound, may help in earlier and more accurate diagnosis. Early intervention reduced fetal mortality but without influence on maternal mortality. Maternal mortality did not depend on the use of X-ray imaging, perforation location, delivery type, trimester of presentation, and maternal age. Exploratory laparoscopy was never performed during pregnancy, only postpartum.

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INTRODUCTION

Peptic ulcer disease (PUD) is a common medical condition caused by hydrochloric acid that breaks down the mucosa and penetrates the submucosa, causing tissue damage. Recurrent symptoms are due to untreated underlying causes [*Helicobacter pylori* (*H. pylori*) infection or nonsteroidal anti-inflammatory drugs (NSAID) consumption][1]. It includes gastric and duodenal ulcers, and delayed treatment leads to high mortality and morbidity[2]. PUD symptoms are non-specific, delaying the diagnosis. Duodenal ulcers often present with night-time abdominal pain or hunger-associated epigastric pain. In contrast, there is an increase in pain for gastric ulcers, which is not observed in duodenal ulcers.

Currently, a modified Johnson classification of PUD is used. Type I includes ulcers along the body of the stomach, most often along the lesser curve at the incisura angularis, not associated with acid hypersecretion. Type II includes ulcers in the body in combination with duodenal ulcers associated with acid over-secretion. Type III includes an ulcer in the pyloric channel within 3 cm of the pylorus, associated with acid over-secretion. Type IV includes proximal gastroesophageal ulcers. Type V can occur throughout the stomach and is associated with chronic NSAID use. Due to the rarity of the disease and the restricted use of gastroscopy, there are no data on the incidence of these PUD types in pregnancy.

PUD and its complications, such as perforated peptic ulcer (PPU), are extremely rare in pregnancy: 1-6/23000 pregnancies[3,4]. Lower rates of PUD and PPU than in the general population are partly due to healthier habits, such as no smoking, reducing stressful activities, and a balanced diet. At the same time, the primary hormone that promotes pregnancy, progesterone, raises the production of protective gastric mucus. In addition, estrogen reduces gastric acid secretion[5].

PUD diagnosis in pregnancy and puerperium is often delayed because clinical presentation during pregnancy, or puerperium, interferes with common symptoms during pregnancy, such as stomach pain, nausea, vomiting, gastroesophageal reflux disease, and pregnancy or delivery complications[6].

Also, pregnant women with PUD have a higher incidence of adverse newborn and obstetric outcomes. These include congenital abnormalities, preterm birth, premature rupture of membranes, placental abruption, preeclampsia/eclampsia, intrauterine growth restriction, intrauterine fetal death, or maternal death[7]. All these conditions can mask the underlying cause, delaying the diagnosis.

Case reports and retrospective clinical series are used to evaluate the incidence of PUDs and PPUs in pregnancy, but they are limited due to the lack of data. Also, there are insufficient data on the impact of PPUs in pregnancy and puerperium on maternal and neonatal morbidity and mortality. Our analysis aimed at presenting the most extensive systematic review of cases of PPU in pregnancy and puerperium.

MATERIALS AND METHODS

We searched PubMed, PubMed Central, and Google Scholar and analyzed the collected articles, following preferred reporting items for systematic reviews and meta-analysis[8]. The search items included: 'ulcer', 'PUD', 'pregnancy', 'puerperium', 'postpartum', 'gravid', 'labor', 'perforated ulcer', 'stomach ulcer', 'duodenal ulcer', 'peptic ulcer'. Additional studies were extracted by reviewing reference lists of the retrieved studies. We included all available full-text cases and case series. Of the 60 cases identified in our initial search, we excluded 14 due to duplicated, overlapping, or insufficient data, spontaneous stomach rupture or perforation diagnosed at the time of surgery, and patients who were not pregnant or not in the puerperium. After manually reviewing all the cases for eligibility, three additional cases were excluded from the initial search (one with stomach tumor perforation and two abstract-only cases with insufficient information). Finally, 43 cases of PPU in pregnancy and the puerperium met the criteria.

Our goal was to summarize all reported cases of PPU in pregnancy and puerperium and identify predictive factors for early diagnosis and treatment. Our second objective was to identify an association between the diagnosis and maternal/neonatal outcomes. This study is exempt from ethics approval as we collected data from published cases.

Data extraction

Two authors independently reviewed the extracted data from the included articles. Pre-defined criteria were established to ensure the maximum reliability of the collected data.

Obstetric data included maternal age, gestational age, and parity. Clinical/patient characteristic data included gastric risk factors, history of symptoms, and duration of symptoms. Diagnostic data included signs of clinical presentation, clinical presentation, radiology findings, and time of perforation in correlation with delivery. Other parameters collected were differential diagnosis, mother and child outcomes, (season) part of the year, type of delivery, type of surgery performed, time from delivery to operation or vice versa, intraabdominal access, location of ulcer perforation, and preoperative endoscopic diagnostic findings.

Statistical analysis

All statistical data were processed using JASP Team (2024), JASP (Version 0.18.3). We calculated means and SDs, medians, and interquartile ranges for continuous data. For categorical data, we calculated frequencies and proportions. A *t*-test was applied to continuous variables, while χ^2 tests or Fisher's exact tests were used for categorical variables.

RESULTS

From the 60 cases identified in our initial search (Figure 1), 43 cases of PPU in pregnancy and puerperium fulfilled the criteria. The data from individual case reports are summarized in Supplementary Table 1.

The mean maternal age was 30.9 years (95% confidence interval: 27.9-32.3 years); 36.6% were multiparous, and 63.4% were nulliparous or primiparous. Multiparas were significantly older than primiparas ($P < 0.05$). Peptic ulcer perforated in 19/43 (44.2%) patients postpartum and 24/43 (55.8%) patients antepartum. Antepartum incidence increased as the pregnancy advanced in these patients, 55.8% were antepartum cases: 2.3% presented in the first, 7% in the second, and 46.5% in the third trimester (Table 1); Postpartum patients presented within the first 8 postpartum days. Parity was not associated with the trimester of presentation. Most antepartum cases (81.8%) occurred in the third trimester (Figure 2). Most women presented with duodenal (76.7%) compared to gastric ulcers (23.3%).

Symptomatology

The most common symptoms were abdominal pain 41/43 (95.3%) and vomiting 28/43 (65.1%), with 26/43 (60.5%) presenting with both symptoms (Table 2). Moreover, 37.2% had a history of dyspepsia, peptic ulcer, gastric surgery, or *H. pylori* infection (Table 3). The most common clinical signs were abdominal tenderness (72.1%), abdominal distension (48.84%), and abdominal rigidity (34.9%) (Table 4). Six patients experienced symptoms lasting < 12 hours, five had symptoms for 12-24 hours, and 22 had symptoms > 24 hours.

Diagnosis

A plain abdominal X-ray was performed in 11/43 (25.6%), with positive findings in 10/11 (90.9%) as free air under the diaphragm. X-ray imaging did not influence maternal mortality (χ^2, $P = 0.556$). When plain X-ray was not used, fetal mortality was 46.15%, while with plain X-ray use, there was no fetal mortality (sample sizes; $n = 13$, $n = 4$). Due to the small sample size, this difference is insignificant (χ^2, $P = 0.091$).

Abdominal ultrasound was performed in 10/43 (23.6%) and was positive in 8/10 (80%), showing free intraperitoneal fluid. The use of ultrasound did not influence maternal mortality (χ^2, $P = 0.296$) or fetal mortality (33.3% *vs* 36.4%; χ^2, $P = 0.091$; Fischer's exact test, $P = 1.00$) (Table 5).

In 15 cases, other diagnoses led to the indications for explorative laparotomy. In 2 cases[9,10], explorative laparoscopy was performed in postpartum PPU. Explorative laparoscopy was never performed during pregnancy.

Vaginal examination was performed in 13/43 (30.3%) cases and was normal in 12/13 (92.3%), one patient had prolapsed placental cord.

Table 1 Baseline information, *n* (%)

Baseline information	
Mean maternal age, years	30.9 (95%CI: 27.9-32.3)
Multiparous (*n* = 38)	15 (39.5)
Primiparous (*n* = 38)	17 (44.7)
Nulliparous (*n* = 38)	6 (15.8)
Antepartum ulcer perforations (*n* = 43)	24 (55.8)
Postpartum ulcer perforations (*n* = 43)	19 (44.2)
First-trimester presentation (*n* = 43)	1 (2.3)
Second-trimester presentation (*n* = 43)	3 (7)
Third-trimester presentation (*n* = 43)	20 (46.5)
Duodenal ulcers (*n* = 34)	26 (76.5)
Gastric ulcers (*n* = 34)	8 (23.5)

CI: Confidence interval.

Table 2 Clinical presentation of perforated peptic ulcer in pregnancy, *n* (%)

Group	Abdominal pain	Nausea/vomiting	Hematemesis	Diarrhea	Jaundice	Constipation
Antepartum (*n* = 19)	18 (94.7)	14 (73.7)	3 (15.8)	0 (0)	0 (0)	0 (0)
Postpartum (*n* = 24)	24 (100)	17 (70.8)	3 (12.5)	2 (8.3)	2 (8.3)	4 (16.7)

Table 3 Maternal medical history related to peptic ulcer, *n* (%)

Maternal medical history	
Dyspepsia (*n* = 43)	12 (27.9)
History of ulcer (*n* = 43)	3 (7)
Eclampsia/preeclampsia (*n* = 43)	6 (14)
None (*n* = 43)	14 (32.6)
Unknown (*n* = 43)	8 (18.6)

Table 4 Clinical examination of perforated peptic ulcer in pregnancy, *n* (%)

Group	Abdominal tenderness	Abdominal rigidity	Abdominal distension	Absence of peristalsis
Antepartum (*n* = 19)	17 (89.5)	7 (36.8)	4 (21.1)	5 (26.3)
Postpartum (*n* = 24)	17 (70.8)	5 (20.8)	16 (66.7)	5 (20.8)

Treatment

Suturing of the perforated site was the method of choice (38/43; 88.4%), with partial gastrectomy performed in 2 cases (4.7%). Frequencies for types of surgical operations are listed in Table 6.

Maternal and fetal outcome

In 31/39 cases, the time from delivery to surgery or vice versa was > 24 hours. Spontaneous vaginal delivery was completed in 20, induced vaginal in 4, and C-section in 16 cases. Outcomes and child and maternal mortality were not related to delivery type, partly due to the small number of cases. The maternal mortality was not related to the trimester of presentation. Maternal age did not influence maternal outcome (30.1 *vs* 30.1 years; *U* test, $P = 0.988$). The gestational week of presentation did not influence fetal mortality (test of log. regression, $P = 0.159$). Depending on the PPU symptoms duration, maternal mortality was 23.1% for symptoms of < 12 hours ($n = 13$) and 37.5% for symptoms > 24

Table 5 Diagnostic imaging and examination, *n* (%)

Diagnostic	
Plain abdominal X-ray (*n* = 43)	11 (25.6)
Positive X-ray findings (*n* = 11)	10 (90.9)
Abdominal ultrasound (*n* = 43)	10 (23.6)
Positive findings (*n* = 10)	8 (80)
Performed vaginal examination (*n* = 43)	13 (30.3)
Normal (*n* = 13)	12 (92.3)
Computed tomography (*n* = 43)	3 (7)

Table 6 Frequencies of surgical procedure

Surgical procedure	Frequency	Percent (%)
Primary closure	17	39.5
Graham's patch	16	37.2
Primary closure with omentoplasty	3	7.0
Modified Graham's patch	2	4.7
Partial gastric resection	2	4.7
No procedure	3	7.0

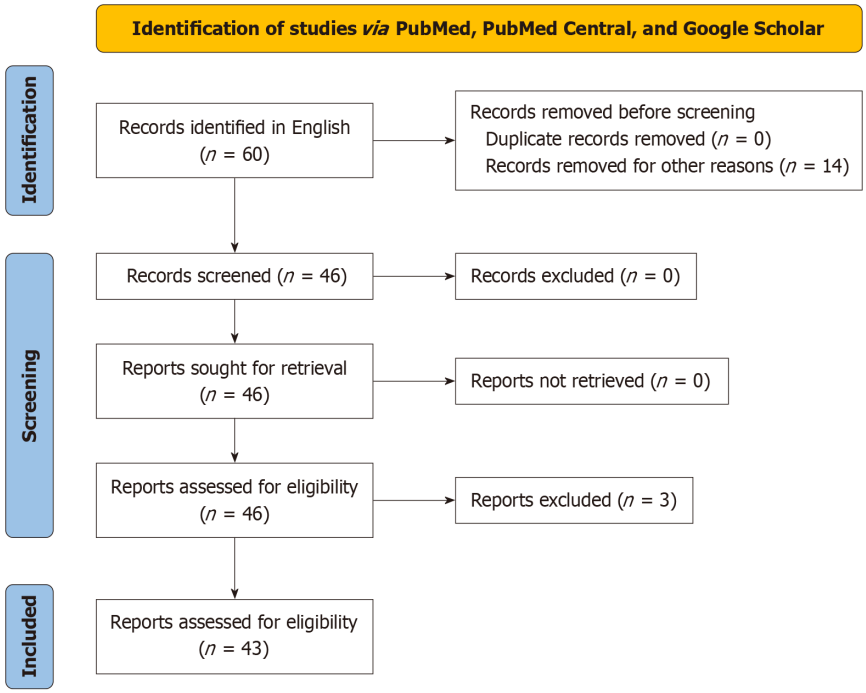


Figure 1 Preferred reporting items for systematic reviews and meta-analysis flow diagram.

hours (*n* = 16), without statistically significant difference (Fischer's exact test, *P* = 0.706). Symptoms lasting 12-24 hours did not result in maternal death. Maternal mortality for duodenal and gastric perforation was 26.9% (7/26) and 25% (2/8), respectively. Maternal mortality did not depend on the perforation location (χ^2, *P* = 0.934).

Fetal mortality was analyzed for patients with symptoms < 12 hours, then with 12-24 hours and > 24 hours. For the first two groups, there were no fetal deaths recorded (8 cases), and fetal mortality for the > 24 hours group was 66.7%, with a statistically significant difference (χ^2, *P* = 0.004; Fischer's exact test, *P* = 0.009). The fetal mortality was 34.8%, and all fetal deaths were during gestational weeks 24-32 (Table 7).

Table 7 Fetal death by gestational week at presentation

Gestational week at presentation	Number of fetal death outcomes out of total cases by week
15	0/1
20	0/1
24	1/1
28	2/2
31	3/3
32	2/3
34	0/2
35	0/1
36	0/3
38	0/2
39	0/2
41	0/1
43	0/1

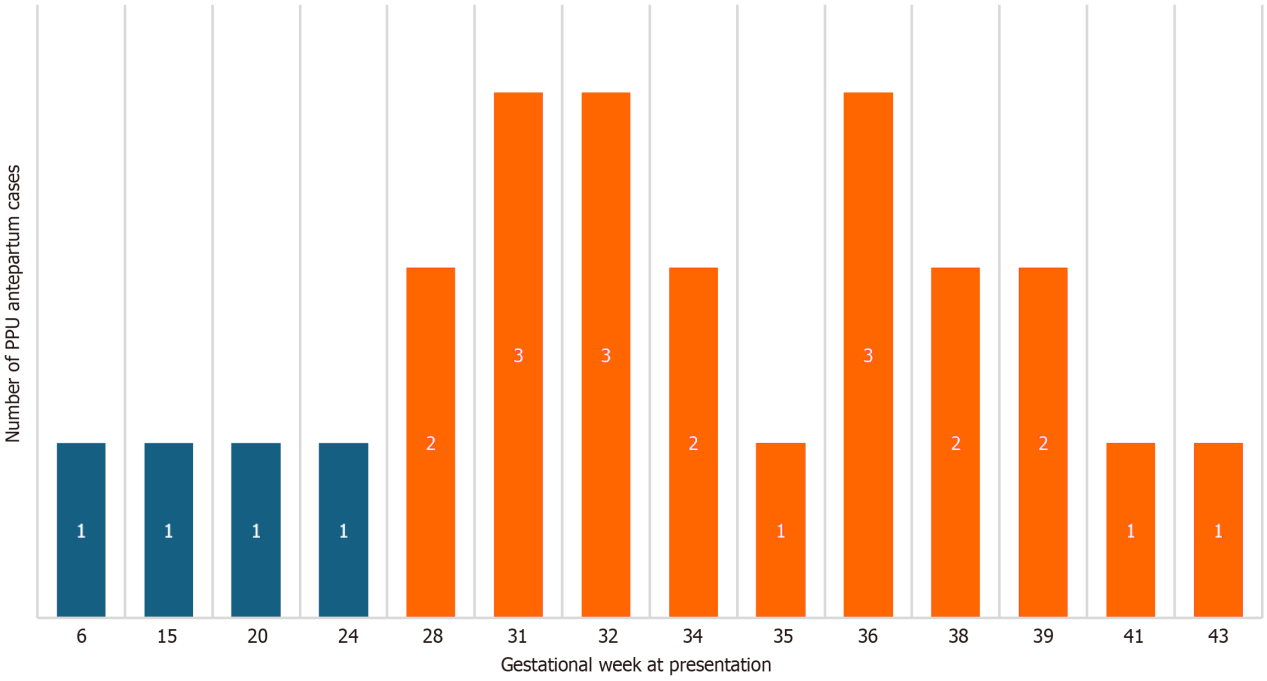


Figure 2 Antepartum perforated peptic ulcers by gestational week. The red bars represent cases from the third trimester. PPU: Perforated peptic ulcer.

DISCUSSION

PPUs are uncommon throughout pregnancy and puerperium, leading to delays in diagnosis and surgical intervention[4,11,12]. By systematically analyzing all potential parameters, our study aimed to provide valuable insights into the clinical characteristics, risk factors, and outcomes of PPUs during pregnancy and the puerperium, ultimately guiding management strategies and potentially reducing associated morbidity and mortality.

Considering the extremely rare occurrence of PPU in pregnancy, studies are scarce. Robin Burkitt documented only three perforated duodenal ulcers in the United Kingdom over 13 (1948-1961) years[13]. In 1962, Lindell and Tera[14] reviewed the literature and reported 14 cases of PPUs during pregnancy, with 100% maternal mortality until their case. In that era, women represented only 10.6% of patients with PPU in the general population[15]. Interestingly, in that era, 50% of women with pregnancy symptoms became asymptomatic during pregnancy[16].

Furthermore, Shirazi *et al*[17], in 2020, reported their 4 cases of post-cesarean PPU surgically repaired with 50% maternal mortality and collected an additional 8 cases of post-cesarean PPU.

Our study aimed to determine crucial parameters concerning PPU during pregnancy and postpartum. When the whole period of our review is divided into three similar long periods (1939-1970, 1971-2000, and 2000-), only three cases were published in the middle period. Evidently, it occurs in older reproductive women, with a mean age of 31 years. We collected cases from 1939 when first pregnancies began at a younger age. Despite this, PPU is more common in nulliparous or primiparous. Half of the patients presented antenatally and the other half postnatally. Most antepartum cases occur in the third trimester, leading to delayed diagnosis due to non-specific symptoms similar to other pregnancy-related gastrointestinal issues, including nausea and vomiting, hyperemesis gravidarum, gastroesophageal reflux disease, and cholecystitis[18,19]. Antepartum PPU incidence, which included 55.8% of cases, increased with advancing gestation-2.3% in the first, 7% in the second, and 46.5% in the third trimester.

In mice, gastrointestinal transit time is significantly prolonged, and gastric emptying is delayed in the third trimester compared to the postpartum period due to increased progesterone and estradiol levels[20,21]. Increased gastroduodenal mucus levels were found in pregnant rats pretreated with progesterone[22].

The gastroprotective effect of progesterone is maximal in the third trimester when the progesterone level peaks. Exogenous progesterone inhibits the myoelectric and mechanical activity of gastrointestinal smooth muscle. Progesterone relaxes smooth muscle and decreases lower esophageal sphincter pressure[23]. The effect of progesterone on the pyloric sphincter remains unclear. Still, its effect on smooth muscle may affect the prevalence of perforated duodenal ulcers in pregnancy (76.7% *vs* 23.3%). Also, immunologic tolerance during pregnancy might permit *H. pylori* to colonize the gastric mucosa without immunologic reaction[4]. In patients with PPU, the prevalence of *H. pylori* infection is 65%-70%[24]. Prolactin increases the ulcer index and ulcer score in acetic acid-induced chronic gastric ulcers[25]. These factors may significantly affect the third trimester's high PPU incidence.

The most common symptoms were abdominal pain and vomiting, while clinical examination revealed abdominal tenderness, rigidity, and distension. The vaginal examination was normal. Other studies confirmed these common symptoms, including abrupt and severe abdominal pain, tachycardia, nausea, vomiting, pyrexia, dehydration, abdominal tenderness, rebound tenderness, involuntary guarding, abdominal rigidity, hypoactive bowel sounds, and hypotension [26-28]. In the postpartum period, acute abdominal pain caused by PPU may be mistaken for normal post-delivery discomfort or post-cesarean pain, and patients who receive post-cesarean narcotic analgesics may get relief[11]. A third of the patients had previous dyspepsia or stomach-related conditions, with a similar incidence as in the non-pregnant population.

Most women presented with duodenal ulcers (76.7%). In the general population, males have a higher incidence of PPU, and duodenal ulcers are also more common[29,30].

Standard diagnostic imaging with plain abdominal X-ray or transabdominal ultrasound should be used when PPU is suspected. Although the analyzed period was almost a century, a plain abdominal X-ray was performed in 25.6% and an abdominal ultrasound in 23.6%. Interestingly, both methods are highly accurate (pneumoperitoneum in 90.9% and free intra-abdominal fluid in 80%). Although the presence of 'free air' on radiological imaging is strongly symptomatic of a ruptured viscus organ, it may not reveal the cause of pneumoperitoneum[31]. If imaging is not available or inconclusive, a diagnostic laparoscopy should be considered[32]. In our review, explorative laparoscopy was performed only in 2 postpartum cases. Therefore, (diagnostic) laparoscopy is still not a common practice in pregnancy or puerperium.

There are no recommendations for the technique of closure of PPU in pregnancy. In most cases, after primary closure by suturing the perforation site (39.5%), Graham's patch has been the second most preferred surgical technique (37.2%) (Table 7). For a significant period, these procedures had been the standard method for treating PPUs, particularly when most abdominal surgeries were performed using a midline laparotomy approach. Once again, the protective factors of pregnancy and the reduction or elimination of PUD risk factors may lead to smaller perforations, which can be repaired using the previously mentioned surgical technique. Some of these risk factors are modifiable, such as smoking, NSAID use, drinking, gastritis, and active *H. pylori* infection[33,34].

Critical issues are maternal and fetal outcomes. The average duration of symptoms before diagnosis or surgical intervention influences outcomes. Maternal mortality is not associated with symptom duration (23.08% and 37.5%), although the trend is lower with shorter duration of symptoms. Maternal mortality does not depend on the use of X-ray imaging, perforation location, delivery type, trimester of presentation, and maternal age.

Contrary to the maternal outcome, fetal mortality increased (0% and 66.7%, symptoms onset < 24 hours and > 24 hours) with longer symptom duration. Therefore, it is of utmost importance for fetal survival to operate on a gravid patient as early as possible, and always within 24 hours. The fetal mortality was 34.8%, and all fetal deaths were during gestational weeks 24-32.

Such patients should be stabilized quickly with electrolyte correction and extensive fluid resuscitation, followed by emergency surgery. Pregnant patients should not receive enteral nourishment and should be given broad-spectrum antibiotics[4]. As in the general population, it is a surgical emergency and delayed surgical treatment leads to short-term mortality of up to 30%[35,36], similar to maternal mortality in this review.

Limits of the study

It was challenging to know the exact time the perforation occurred. Many patients had epigastric pain for several days, sometimes even weeks, before PPU developed. The perforation time was estimated when the patients developed severe and sharp pain, much more painful than during previous days. Also, PPU indicators were increased pulse during the disease or the timing of collapse before going to an emergency department. A limitation is the analyzed period of almost a century, although most diagnostic modalities and treatment options for PPU have not changed much.

CONCLUSION

PPU during pregnancy and puerperium may be mistaken for more common conditions, and the correct diagnosis was frequently delayed. Approximately 1/3 of the women had dyspeptic symptoms before ulcer perforation. Almost all patients presented during the third trimester or the first 8 days postpartum. Antepartum incidence increased as the pregnancy advanced. Common symptoms were abdominal tenderness and distension. Early and mandatory imaging, including plain abdominal X-ray and abdominal ultrasound, may help in earlier and more accurate diagnosis. Early intervention reduces fetal mortality but not maternal mortality. Maternal mortality did not depend on the use of X-ray imaging, perforation location, delivery type, trimester of presentation, and maternal age. Explorative laparoscopy was never performed during pregnancy, only postnatally.

FOOTNOTES

Author contributions: Augustin G and Krstulovic J designed the research; Tavra A, Hrgović Z, and Krstulovic J performed the research; Augustin G, Tavra A, and Hrgović Z analyzed the data; Hrgović Z, Tavra A, Krstulovic J, and Augustin G wrote the paper.

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SCIENTOMETRICS

Visualizing global progress and challenges in esophagogastric variceal bleeding

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Abstract

BACKGROUND

Esophageal and gastric variceal bleeding is a catastrophic complication of portal hypertension, most commonly caused by cirrhosis of various etiologies. Although a considerable body of research has been conducted in this area, the complexity of the disease and the lack of standardized treatment strategies have led to fragmented findings, insufficient information, and a lack of systematic investigation. Bibliometric analysis can help clarify research trends, identify core topics, and

reveal potential future directions. Therefore, this study aims to use bibliometric methods to conduct an in-depth exploration of research progress in this field, with the expectation of providing new insights for both clinical practice and scientific research.

AIM
To evaluate research trends and advancements in esophagogastric variceal bleeding (EGVB) over the past twenty years.

METHODS
Relevant publications on EGVB were retrieved from the Web of Science Core Collection. VOSviewer, Pajek, CiteSpace, and the bibliometrix package were then employed to perform bibliometric visualizations of publication volume, countries, institutions, journals, authors, keywords, and citation counts.

RESULTS
The analysis focused on original research articles and review papers. From 2004 to 2023, a total of 2097 records on EGVB were retrieved. The number of relevant publications has increased significantly over the past two decades, especially in China and the United States. The leading contributors in this field, in terms of countries, institutions, authors, and journals, were China, Assistance Publique-Hôpitaux de Paris, Bosch Jaime, and *World Journal of Gastroenterology*, respectively. Core keywords in this field include portal hypertension, management, liver cirrhosis, risk, prevention, and diagnosis. Future research directions may focus on optimizing diagnostic methods, personalized treatment, and multidisciplinary collaboration.

CONCLUSION
Using bibliometric methods, this study reveals the developmental trajectory and trends in research on EGVB, underscoring risk assessment and diagnostic optimization as the core areas of current focus. The study provides an innovative and systematic perspective for this field, indicating that future research could center on multidisciplinary collaboration, personalized treatment approaches, and the development of new diagnostic tools. Moreover, this work offers practical research directions for both the academic community and clinical practice, driving continued advancement in this domain.

Key Words: Esophagogastric variceal bleeding; Liver cirrhosis; Portal hypertension; Non-cirrhotic portal hypertension; Bibliometrics; Visualization

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Core Tip: This study provides a comprehensive analysis of research trends in esophagogastric variceal bleeding over the past two decades through bibliometric methods. By systematically reviewing a wide range of publications, it identifies key areas of focus, particularly in risk assessment and diagnosis, which are crucial for advancing clinical decision-making. Additionally, the findings highlight the importance of emerging technologies and innovative approaches in the management of this condition. Future research directions may focus on optimizing diagnostic techniques, personalized treatment strategies, and fostering multidisciplinary collaboration to improve patient outcomes and enhance understanding of esophagogastric variceal bleeding.

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INTRODUCTION

Esophagogastric variceal bleeding (EGVB) is a severe complication arising from various forms of portal hypertension (PH), with liver cirrhosis being the most frequent underlying cause[1]. Liver cirrhosis ranks as the 11th most common cause of death globally and the 3rd leading cause of mortality among individuals aged 45-64, accounting for approximately one million deaths annually; it affects men and women at a ratio of 6:4[2]. In addition to liver cirrhosis, noncirrhotic PH (NCPH), including conditions such as portosinusoidal vascular liver disease and portal vein thrombosis (PVT), can also result in EGVB[3]. In patients with cirrhosis, the incidence of esophageal and gastric varices (GV) is approximately 50%, with 10%-30% of these patients experiencing EGVB each year. The mortality rate for the first bleeding episode ranges from 20% to 35%, and the six-week mortality rate can reach 15%-20%. EGVB is extremely severe and, if not promptly and effectively controlled, can lead to serious clinical consequences[4]. However, for EGVB patients, conventional treatment methods are often unable to reverse the pathological basis of portal vein blood flow obstruction

[5], which continues to pose significant challenges for the prevention and management of EGVB.

These challenges are reflected not only in the complexity of clinical treatments but also in the current state of research in this field. In recent years, research on EGVB has gradually increased, but the fragmentation and complexity of the literature make it difficult for researchers to comprehensively grasp the progress of EGVB studies. These studies predominantly focus on specific etiologies, treatment methods, or clinical manifestations, yet they lack a systematic perspective to integrate existing findings, thereby failing to reveal the main directions and potential gaps in EGVB research.

Bibliometric methods, which employ mathematical and statistical techniques for qualitative and quantitative analysis of publications, can objectively provide a unique perspective that comprehensively highlights the current state of EGVB research and reveals the context of related studies. These methods not only enable researchers to identify the countries or regions, institutions, and authors from which the publications originate but also allow for the summarization and categorization of the research status, publication trends, future research hotspots, academic frontiers, and knowledge maps in this field, which holds significant value. Furthermore, bibliometric analysis has been widely applied in research related to liver disease, including liver fibrosis[6,7] and liver cirrhosis[8,9]. However, no such studies have been identified in the field of EGVB. Therefore, this study employs bibliometric analysis methods to comprehensively summarize and review the research status of EGVB over the past two decades for the first time. This approach is expected to help researchers and clinicians gain a better understanding of the current state of EGVB research and to identify new directions for future studies.

MATERIALS AND METHODS

Search strategy

The literature search was performed on June 25, 2024, at the Affiliated Shuguang Hospital of Shanghai University of Traditional Chinese Medicine, utilizing the Web of Science Core Collection (WoSCC). As one of the most comprehensive and authoritative databases, WoSCC is especially well-suited for conducting bibliometric analyses in the fields of natural sciences and medicine. Our search strategy included: Topic = "esophagogastric variceal bleeding" or "esophageal variceal bleeding" or "esophageal gastric variceal bleeding" or "esophageal varices bleeding" or "esophagogastric varices bleeding" or "stomach esophagus varicosity burst hemorrhage" or "esophageal gastric varices bleeding" or "gastroesophageal variceal hemorrhage" or "esophagogastric variceal hemorrhage". The WoSCC was selected as the database, with the search covering the period from January 1, 2004, to December 31, 2023. Only original research articles and review papers were included, and the language was restricted to English. Articles published before January 1, 2004, were excluded. Furthermore, conference abstracts, proceedings papers, editorials, and other article types were also excluded. Figure 1 presents a flowchart detailing the search strategy employed in this study.

Data collection

The bibliographic data retrieved through the query was downloaded from the WoSCC on June 25, 2024. Detailed information, including authors, titles, sources, sponsors, citation counts, accession numbers, abstracts, addresses, document types, and references, was downloaded in TXT format for subsequent analysis. The h-index of the top 10 most prolific authors was obtained from the Web of Science platform. Additionally, the 2023 impact factor (IF) and Journal Citation Report category quartile for 2023 of the top 10 core journals in EGVB research were extracted from Web of Science.

Statistical analysis

This study employed various tools for statistical analysis, including VOSviewer (version 1.6.18), Pajek (version 5.17), CiteSpace (version 6.2.R6), and the Bibliometrix R package (version 4.1.4, running on R version 4.3.3). Information related to authors, institutions, countries, and journals was collected and processed using these tools. Parameters such as the number of articles, IF, centrality, and burst citations/occurrences were analyzed. Productivity was assessed by the number of published articles, enabling the identification of prolific individuals or institutions. The IF was used to gauge the global influence of journals, with data sourced from the 2023 journal citation reports. VOSviewer, a software tool designed for constructing and visualizing bibliometric networks, was employed to analyze collaborative relationships among countries, authors, and institutions, as well as to assess keyword co-occurrence patterns. In addition, VOSviewer, combined with Pajek software, was used for the visualization of author keyword analysis[10]. CiteSpace, a widely-used visualization tool for trend and hotspot research, was employed to conduct burst detection analysis and timeline visualization of keyword clusters[11]. Bibliometrix, an open-source tool based on the R programming language, was used to visualize country collaboration maps[12].

RESULTS

Results annual analysis of publications

Overall, 2097 articles related to EGVB were identified in the WoSCC database between 2004 and 2023, comprising 1791 original articles and 306 reviews. Figure 2 displays the annual number of publications on EGVB, revealing a steady increase in research activity in this field, consistent with the general growth pattern of scientific literature. Compared to other fields, such as liver cirrhosis and its associated immunological factors where publication trends are surging,

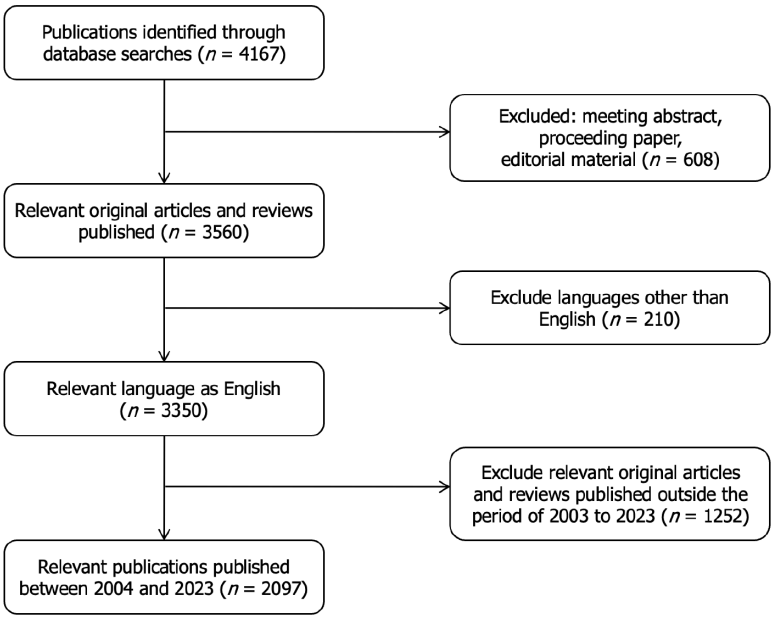


Figure 1 The inclusion and exclusion of publications on esophagogastric variceal bleeding.

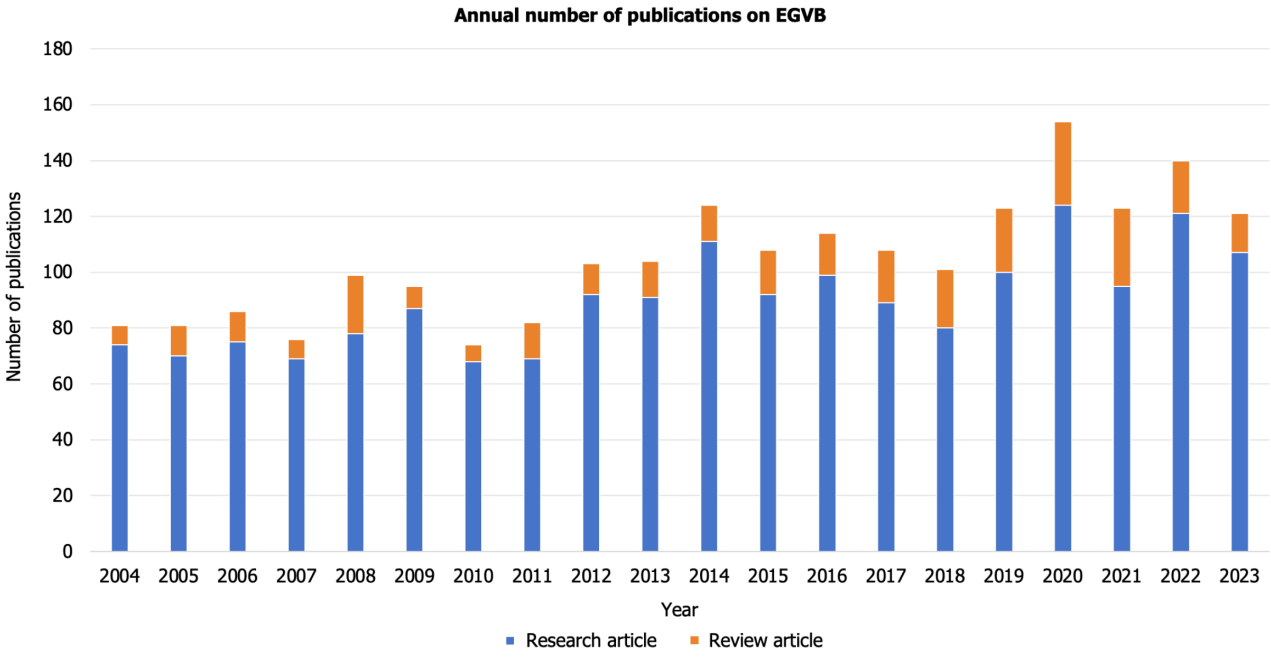


Figure 2 Annual publication count on esophagogastric variceal bleeding. EGVB: Esophagogastric variceal bleeding.

research in the EGVB field has been growing progressively. Despite causing significant clinical consequences, this area currently does not receive adequate attention. Moreover, the number of high-impact journals and their IFs in the EGVB field have not yet reached the level of specialized and mature research areas seen in other disciplines, indicating that research in this field remains to be fully explored[8,9].

Analysis of countries/regions, institutions, authors, and journals frequency

As presented in Table 1, the frequency analysis of countries/regions from 2004 to 2023 indicates that China and the United States are the dominant contributors to EGVB research. The major research hubs are located in Asia, Europe, and North America. It can be observed that the majority of research on EGVB originates from the world's two largest economies, China and the United States. This also indicates that studying EGVB requires substantial funding and talent. Adequate research funding support and robust infrastructure are more conducive to EGVB research. Among the main sponsors are the National Natural Science Foundation of China and the National Institutes of Health of the United States. Besides China and Iran, most of the countries conducting research in this field are developed nations, suggesting that developing countries have started their research in this area relatively late. Based on a comprehensive analysis of

Table 1 Lists the top 10 countries/regions, institutions, authors, and journals contributing to esophagogastric variceal bleeding research

Rank	Country/region	Count	Institution	Count	Author	Count	Journal	Count	2023 IF/JCR partition
1	China	1638	Univ Barcelona	43	Bosch Jaime	31	*World Journal of Gastroenterology*	115	Q1/4.30
2	United States	1391	Capital Med Univ	42	Abraldes Juan g	17	*Journal of Gastroenterology and Hepatology*	61	Q2/3.70
3	Japan	782	Mayo Clin, Natl Yang Ming Univ	34	Berzigotti Annalisa	12	*European Journal of Gastroenterology & Hepatology*	56	Q3/2.30
4	South Korea	644	Univ Milan	33	Garcia-Tsao Guadalupe	11	*Gastrointestinal Endoscopy and Medicine*	46	Q1/6.70, Q2/1.30
5	Australia	540	Shandong Univ	28	Carlos Garcia-Pagan Juan	11	*Journal of Clinical Gastroenterology*	44	Q2/2.80
6	Italy	369	Hosp Clin Barcelona	27	Tripathi Dhiraj	10	*Digestive Diseases and Sciences*	43	Q2/2.50
7	United Kingdom	273	Fudan Univ	26	Garcia-Pagan Juan Carlos	7	*American Journal of Gastroenterology, Hepatology*	40	Q1/8.00, Q1/12.90
8	Belgium	263	Yonsei Univ	24	Stanley Adrian j	5	*Journal of Pediatric Gastroenterology and Nutrition*	37	Q1/2.40
9	Iran	259	Taipei Vet Gen Hosp, Yale Univ	23	Patch David	5	*Journal of Hepatology*	35	Q1/26.80
10	Germany	221	Chang Gung Univ	22	Hayes Peter c.	5	*Endoscopy, BMC Gastroenterology*	31	Q1/11.50, Q2/2.50

IF: Impact factor; JCR: Journal citation reports.

publishing institutions and countries, the most authoritative and central countries and institutions are concentrated in China and the United States. Although China began later than the United States, it has already become a world leader in this research field through strong investments in capital and talent.

The University of Barcelona and Capital Medical University emerge as the most prominent institutions, exhibiting the highest levels of collaboration in EGVB research. The top author with the most publications is Bosch, Jaime from the University of Barcelona, followed by Abraldes Juan G, and Berzigotti Annalisa. Nine out of the top ten authors are from Spain and the United Kingdom. The three leading journals are *World Journal of Gastroenterology*, *Journal of Gastroenterology and Hepatology*, and *European Journal of Gastroenterology and Hepatology*, collectively publishing 508 papers. These journals are predominantly focused on gastroenterology, hepatology, and endoscopy, with some general medical journals also included.

Author, institution, country, and collaboration analysis

A total of 192 authors from 43 countries or regions have published 2097 articles. As shown in Figure 3, the United States and China have the highest number of collaborations, and the United States also maintains close collaborative relationships with Spain, Italy, and France. For these 200 institutions and 190 authors, the total strength of their collaborations with other organizations or authors will be calculated, selecting those organizations and authors that exhibit the highest link strength in the collaboration network, *i.e.*, the most "active" organizations and authors. A basic manifestation of collaboration centrality is the size of the nodes. Typically, nodes with higher centrality (*i.e.*, authors, institutions, or countries that collaborate frequently) are displayed as larger nodes. VOSviewer automatically adjusts the node size based on collaboration frequency or the number of "connections" in the network. Larger nodes usually represent researchers, institutions, or countries that hold more important positions in the collaboration network.

In terms of institutions, Figure 4 identifies six collaborative clusters among the institutions, with the University of Barcelona exhibiting the highest level of collaboration centrality, followed by the University of Milan and Hospital Clínic Barcelona (Figure 4A). Collaboration among authors is relatively close, with five clusters emerging (Figure 4B). Bosch, Jaime demonstrates the highest level of collaboration centrality, followed by Abraldes, Juan G, Carlos Garcia-Pagan, Juan, and Berzigotti, Annalisa.

Citation analysis

As shown in Table 2, the most cited article is the 2017 guideline by the American Association for the Study of Liver Diseases (AASLD), authored by Garcia-Tsao *et al*[13] and published in *Hepatology*, with 1242 citations. The guideline offers evidence-based recommendations for the risk stratification, diagnosis, and management of PH in patients with liver cirrhosis. It emphasizes the use of non-invasive tools, such as transient elastography (TE), for diagnosing clinically significant PH (CSPH) and esophagogastric varices (EGV). Additionally, it advocates for the use of non-selective beta-blocker (NSBB), particularly carvedilol, as the first-line therapy for managing PH[13].

Table 2 Ranking of the top 10 most cited references

Rank	Year	Title	Journal	First author	Citations
1	2017	Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases	*Hepatology*	Garcia-Tsao Guadalupe	1242
2	2006	Diagnosis of cirrhosis by transient elastography (fibroscan): A prospective study	*Gut*	Foucher J	989
3	2004	Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis	*Journal of Hepatology*	Amitrano L	382
4	2015	UK guidelines on the management of variceal haemorrhage in cirrhotic patients	*Gut*	Tripathi Dhiraj	371
5	2004	Influence of portal hypertension and its early decompression by tips placement on the outcome of variceal bleeding	*Hepatology*	Monescillo A	341
6	2006	Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: A systematic review	*Gastroenterology*	D'Amico Gennaro	339
7	2014	Competing risks and prognostic stages of cirrhosis: A 25-year inception cohort study of 494 patients	*Alimentary Pharmacology and Therapeutics*	D'Amico G	315
8	2005	Systematic review: The model for end-stage liver disease - should it replace Child-Pugh's classification for assessing prognosis in cirrhosis?	*Alimentary Pharmacology and Therapeutics*	Cholongitas E	312
9	2015	Causes and consequences of portal vein thrombosis in 1243 patients with cirrhosis: Results of a longitudinal study	*Hepatology*	Nery Filipe	294
10	2011	Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease	*Journal of Cystic Fibrosis*	Debray Dominique	273

The guideline was updated in 2023, with several significant revisions. It now incorporates systematic reviews, evidence quality assessments, and stronger recommendations based on recent research. The updates also include new dosing guidelines for carvedilol to address non-liver-related conditions. Furthermore, the updated guideline establishes a hepatic venous pressure gradient (HVPG) of ≥ 10 mmHg as the diagnostic threshold for CSPH. These additional recommendations are grounded in the latest research, making the guideline more authoritative and applicable in clinical practice[14].

Foucher *et al*[15] published a prospective study in *Gut* in 2006 on the application of FibroScan technology for the diagnosis of liver cirrhosis. Over the subsequent two decades, TE has been widely applied in the field of EGVB and has been incorporated into the Baveno VI consensus[15]. As a non-invasive method, TE demonstrates a strong correlation with liver stiffness measurement (LSM) and HVPG. However, it cannot fully replace HVPG measurement or upper gastrointestinal endoscopy, which remain the "gold standards" for evaluating EGV[16].

Amitrano *et al*[17] investigated the occurrence of PVT in patients with liver cirrhosis and found that PVT is not uncommon among these patients. PVT may present as asymptomatic or with severe symptoms, such as bleeding due to PH or intestinal infarction. Although clinical manifestations are diverse, only the prothrombin gene 20210 mutation showed a significant independent association with PVT, suggesting that this gene mutation may be an important risk factor[17]. The Liver Department of the British Society of Gastroenterology led the development of the "United Kingdom Guidelines On The Management Of Variceal Haemorrhage In Cirrhotic Patients", which focuses on the management of variceal bleeding in patients with liver cirrhosis. This guideline replaces the older version published in 2000, reflecting the latest medical practices and research findings. It primarily includes primary prevention, management of acute variceal bleeding (AVB), secondary prevention, and treatment of GV, but does not address the management of underlying liver diseases or the treatment of variceal bleeding in pediatric patients[18].

Monescillo *et al*[19] explored the impact of PH and early decompression through Transjugular Intrahepatic Portosystemic Shunt (TIPS) on patients with variceal bleeding. The study measured HVPG in 116 cases of AVB patients and found that high-risk patients who underwent TIPS treatment had significantly reduced rates of treatment failure, transfusion requirements, and intensive care unit admissions, along with lower one-year mortality rates. The results indicate that early measurement of HVPG and timely application of TIPS are crucial for high-risk patients, as they can improve treatment outcomes and survival rates[19].

D'Amico *et al*[20] systematically evaluated the impact of reducing the HVPG on variceal bleeding in patients with liver cirrhosis. The results indicated that lowering HVPG to 12 mmHg or achieving a reduction of more than 20% from baseline significantly decreased the risk of bleeding and, when reduced by 20%, significantly lowered mortality rates. Additionally, the study discussed the heterogeneity between different reduction targets, emphasizing the importance of applying these hemodynamic goals in clinical practice. Furthermore, based on a 25-year cohort study involving 494 patients, the research explored the competing risks and prognostic stages of liver cirrhosis, finding that various competing mortality risks are prevalent among patients. By stratifying patients based on risk factors (ascites, bleeding, jaundice, or encephalopathy), their prognosis can be better assessed, and targeted treatment plans can be developed. The authors noted that future research should focus on how to effectively implement these risk assessment models in clinical practice[20].

Cholongitas *et al*[21] examined the effectiveness of the Model for End-Stage Liver Disease (MELD) score compared to the Child-Turcotte-Pugh (CTP) score in prognostically evaluating patients with liver cirrhosis outside of transplant

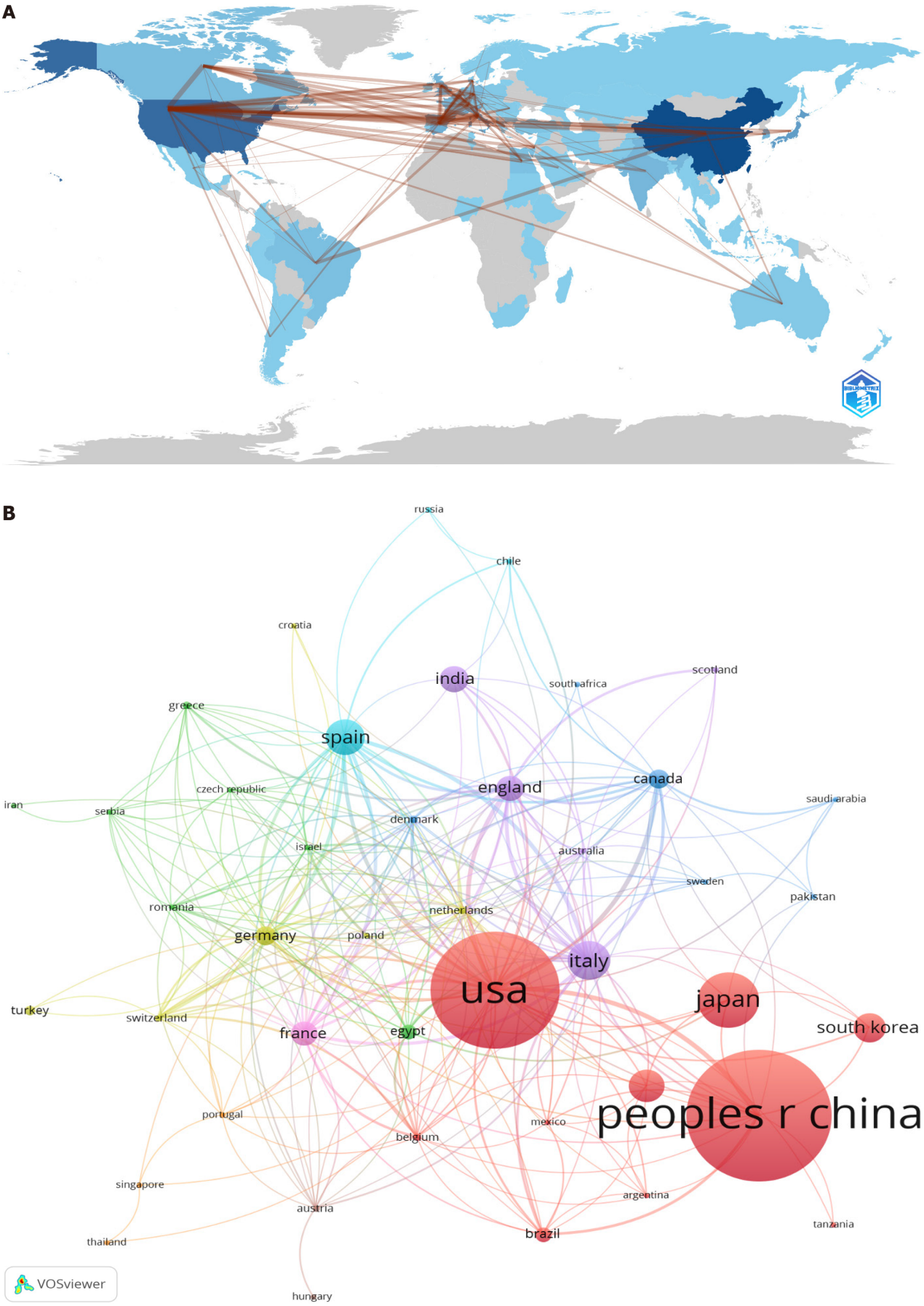


Figure 3 Leading countries/regions. A: Publication distribution and collaborations across countries/regions; B: International collaboration clusters among these countries/regions.

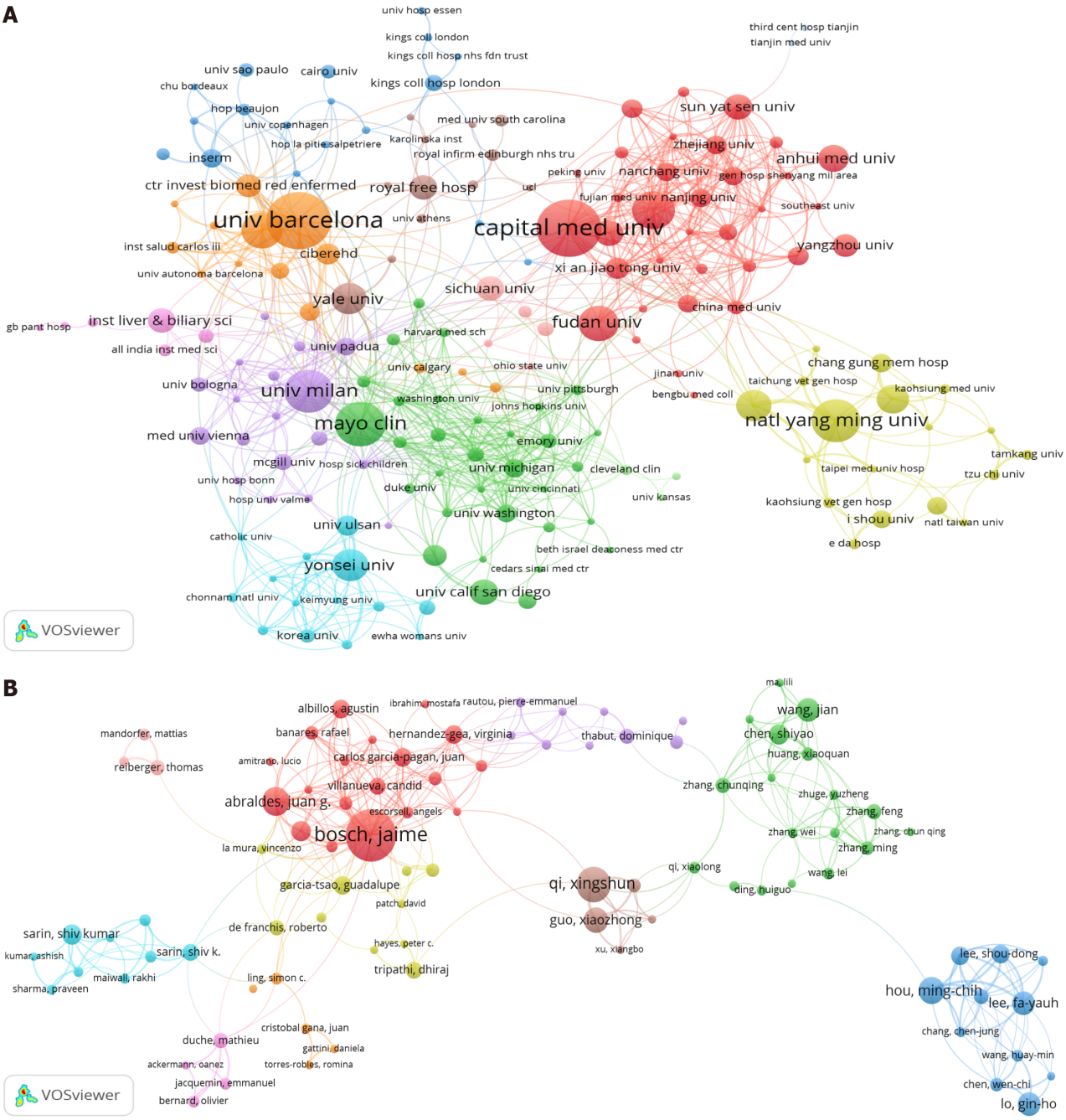


Figure 4 Active institutions and authors. A: Institutional collaboration networks; B: Author collaboration networks.

settings. With the emergence of new therapies, the prognosis of liver cirrhosis patients has attracted widespread attention. The MELD score is currently used to allocate patients on the liver transplant waiting list, but its effectiveness in other contexts remains controversial. In studies involving 1360 patients with liver cirrhosis, only five indicated that the MELD score was superior to the CTP score in predicting 3-month mortality, while there was no significant difference in predicting 12-month mortality. A study involving 2569 patients showed no significant difference between short-term and long-term prognostic scores. In a study of 411 Liver cirrhosis patients with variceal bleeding, there was also no difference in prognostic performance between the MELD and CTP scores. According to existing literature, in non-transplant settings, the MELD score does not outperform the CTP score. Further evaluation of the modified CTP score and the MELD score is necessary to determine their applications in clinical practice[21].

PVT in liver cirrhosis may be a cause or a consequence of disease progression. The study analyzed 1243 patients with liver cirrhosis without PVT, with a follow-up period of 47 months. It was found that the cumulative incidence of PVT was 10.7%, and its occurrence was significantly associated with baseline esophageal varices (EV) and prothrombin time, but not with recent progression of liver disease. The conclusion indicates that in patients with liver cirrhosis, the development of PVT reflects the severity of liver disease but does not lead to further progression of the disease[22].

After conducting an in-depth analysis of the literature related to liver cirrhosis and PH, we can extract several important clinical insights from the highly cited papers. First, the most frequently cited studies indicate that early assessment using non-invasive detection techniques, such as TE (FibroScan) and HVPG, holds significant value for risk

stratification and management of patients with liver cirrhosis. These techniques are particularly valuable in providing crucial guidance for monitoring variceal bleeding and PVT. For instance, the guidelines and related research by Garcia-Tsao *et al*[13] offer a systematic approach to the diagnosis and treatment of PH in liver cirrhosis, and these findings have a substantial impact on clinical practice. Additionally, HVPG, as a key hemodynamic indicator, is widely recognized for its role in prognostic evaluation and treatment decision-making. Timely therapeutic interventions, such as TIPS, have been shown to significantly reduce patient mortality and treatment failure rates[23].

However, despite the aforementioned studies achieving certain successes in clinical applications, issues remain, such as differences in the effectiveness of various clinical scoring systems (*e.g.*, MELD and CTP) in evaluating the prognosis of liver cirrhosis. Future research should further explore how to optimize existing scoring models to enhance their accuracy and practicality in clinical practice. Additionally, with the continuous advancement of new therapeutic methods, integrating these new findings and improving the clinical applicability of existing guidelines will be important directions for future research.

In summary, these highly cited papers not only provide clinicians with an in-depth understanding of liver cirrhosis and PH but also emphasize the importance of early intervention, precise assessment, and individualized treatment. Further research should continue to deepen these findings and promote the translation of more effective diagnostic and therapeutic strategies into clinical practice. The usage frequency within 180 days reflects the extent to which the articles meet users' information needs. This can be verified by users clicking on the full-text links on publisher websites or saving metadata for future use. By sorting the results retrieved from the WoSCC accordingly, this assessment can be achieved. Although it takes time for high usage frequency to translate into high citations, new literature is more likely to be adopted by researchers due to its novelty. Meanwhile, older articles with high citation rates can also drive a resurgence in usage frequency. Therefore, the usage frequency within 180 days can, to some extent, reflect current research hotspots and cutting-edge areas[24].

As shown in Table 3, the article with the highest usage frequency within 180 days is the study by Seven *et al*[25], which compared the efficacy of endoscopic ultrasound-guided coil deployment with and without cyanoacrylate injection in the treatment of GV. The results demonstrated minimal differences between the two methods in terms of rebleeding rates, need for reintervention, or overall survival[25]. The second article, published in *Journal of Digital Imaging*, is by Wang *et al* [26], who integrated endoscopic images and clinical data using machine learning to predict the likelihood of esophageal variceal bleeding (EVB) in patients[26]. Additionally, Gao *et al*[27] developed a machine learning model utilizing contrast-enhanced computed tomography (CT) to predict clinical outcomes in patients with AVB associated with liver cirrhosis [27]. Wang *et al*[28] created an artificial intelligence (AI) system by establishing multiple machine learning models, offering a novel interpretable system for identifying risk factors in EGVB[28]. Whether the integration of machine learning and AI technologies will enhance the accuracy of predicting bleeding risk in EGVB patients remains to be determined. The AASLD and the Chinese Medical Association have also updated their guidelines, reflecting the medical community's widespread attention to EGVB and providing new standards for the future diagnosis, treatment, and management of EGVB[14,29].

Keyword frequency analysis

Keyword frequency is a key indicator that directly reveals the research focus, hotspots, and emerging trends in a field. Figure 5 lists the top 50 keywords extracted using the Bibliometrix package, and synonymous terms were combined for analysis.

Keyword co-occurrence analysis

There is a certain correlation among the keywords presented in the text, which can be represented by their co-occurrence frequency. It is generally believed that the more keyword themes appear within the same document, the closer the relationship between these two themes. Among the top 50 keywords, three clusters were identified based on keyword contribution, as shown in Figure 5. After excluding title-related keywords such as “esophageal varices”, “hemorrhage”, “variceal bleeding”, “gastric varices”, and “gastroesophageal varices”, the core keywords of EGVB include “portal hypertension”, “management”, “cirrhosis”, “risk”, “prevention”, and “diagnosis”. It is evident that the research focus of EGVB centers on studying its risk factors and diagnostic methods.

Keyword burst analysis

A keyword burst refers to a rapid rise in the frequency of a keyword over a specific period, effectively highlighting research hotspots and emerging frontiers in the field during that time (Figure 6). CiteSpace was used to analyze the keyword burst for studies related to EGVB from 2004 to 2023. The keyword burst detection can track research frontiers, and several emerging research topics have already been identified. The Figure 6 displays the top 25 keywords with the highest burst intensity. The blue line represents the timeline, while the red segments indicate the period when the burst occurred. “Year” marks the first appearance of the keyword, “Begin” and “End” show the start and end years of the burst, and “Strength” indicates the intensity of the burst. This figure highlights the research frontiers over different periods. After excluding title-related keywords, “risk” became a research focus from 2019 to 2023, and “diagnosis” has been at the forefront of research from 2021 to 2023.

Keyword timeline

In bibliometric studies, the keyword timeline is a crucial indicator. The strongest burst segments of citations are considered the knowledge base of research frontiers. The clusters along the horizontal timeline are displayed in Figure 7, a timeline visualization from CiteSpace. Each cluster is shown from left to right, with the publication timeline legend

Table 3 Top 10 articles by 180-day usage

Rank	Year	Title	Journal	First author	Usage count
1	2022	Comparison of endoscopic ultrasound-guided coil deployment with and without cyanoacrylate injection for gastric varices	*Arab Journal of Gastroenterology*	Seven G	11
2	2023	Automated multimodal machine learning for esophageal variceal bleeding prediction based on endoscopy and structured data	*Journal of Digital Imaging*	Wang Y	9
3	2023	Prevalence, clinical characteristics, and outcomes of spontaneous portosystemic shunt in patients with hepatitis b-related cirrhosis: A multicenter study from china	*Digestive and Liver Disease*	Ke Q	8
4	2022	Optimal treatment for patients with cavernous transformation of the portal vein	*Frontiers in Medicine*	Wei B	7
5	2015	Intraoperative salvage endoscopy performed during orthotopic liver transplantation due to esophageal bleeding	*Videosurgery and Other Miniinvasive Techniques*	Kobryn K	7
6	2023	AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis	*Hepatology*	Kaplan DE	6
7	2023	Guidelines for the management of esophagogastric variceal bleeding in cirrhotic portal hypertension	*Journal of Clinical and Translational Hepatology*	Xu XY	6
8	2023	An imaging-based machine learning model outperforms clinical risk scores for prognosis of cirrhotic variceal bleeding	*European Radiology*	Gao Y	6
9	2023	Diagnosis and management of esophagogastric varices	*Diagnostics*	Pallio S	6
10	2022	An interpretable artificial intelligence system for detecting risk factors of gastroesophageal variceal bleeding	*NPJ Digital Medicine*	Wang J	5

AASLD: American Association for the Study of Liver Diseases.

located at the top. Keywords are anchored to the year they first appeared in the analyzed dataset. Once a keyword emerges, it remains fixed to its initial year, even if it continues to appear in later papers; it will only be displayed in the year of its first occurrence. Keywords are clustered and numbered sequentially, starting from 0, with Cluster 0 being the largest. In this study, the largest cluster is 0, "PVT," reflecting a major research focus in recent years. This is followed by Cluster 1, "GV," 2, "endoscopic sclerotherapy," 3, "isosorbide mononitrate," 4, "transjugular intrahepatic portosystemic shunt," and 5, "diagnosis." Some clusters have remained active until 2023. The keyword timeline diagram, created using CiteSpace, reflects the changing trends in research topics over time in this field.

DISCUSSION

General situation

We performed a quantitative analysis of the EGVB research literature published over the past 20 years, which revealed a consistent upward trend in the number of publications and strong connections to conditions such as PH, PVT, liver fibrosis, liver cirrhosis, and NCPH. As one of the most severe complications of chronic liver disease, EGVB continues to attract considerable attention in hepatology research. Summarizing the trends in EGVB research helps researchers understand recent developments and hotspots, guiding future studies. In terms of publication volume, the fields of gastroenterology and hepatology are the most representative. Jaime Bosch from the Hospital Clínic of Barcelona, Spain, is the most prolific expert, whereas the University of Barcelona leads in institutional output. China ranks first in terms of the number of publications, followed by the United States, with both countries significantly outpacing others. As shown in Figure 3B, China and the United States also present the strongest collaborative ties. This information allows us to identify authors working in similar research directions, providing a reference for collaboration and communication between researchers.

Core journals and important literature

The core journals in the field of EGVB include the *World Journal of Gastroenterology*, the *Journal of Gastroenterology and Hepatology*, the *European Journal of Gastroenterology and Hepatology*, *Gastrointestinal Endoscopy and Medicine*, and the *Journal of Clinical Gastroenterology*. These journals have significant influence and academic reputation within the EGVB research domain, and we can expect to identify more cutting-edge research topics published in these journals in the future. The most cited and highly recognized article in this field is by Garcia-Tsao *et al*[13], published in *Hepatology*, titled "Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by AASLD" with 977 citations. Although this article was published in 2017, it presented important consensus recommendations. The guidelines have been updated to the 2023 version, offering clear recommendations for both primary and secondary prevention of EGVB in patients with cirrhosis[13,14].

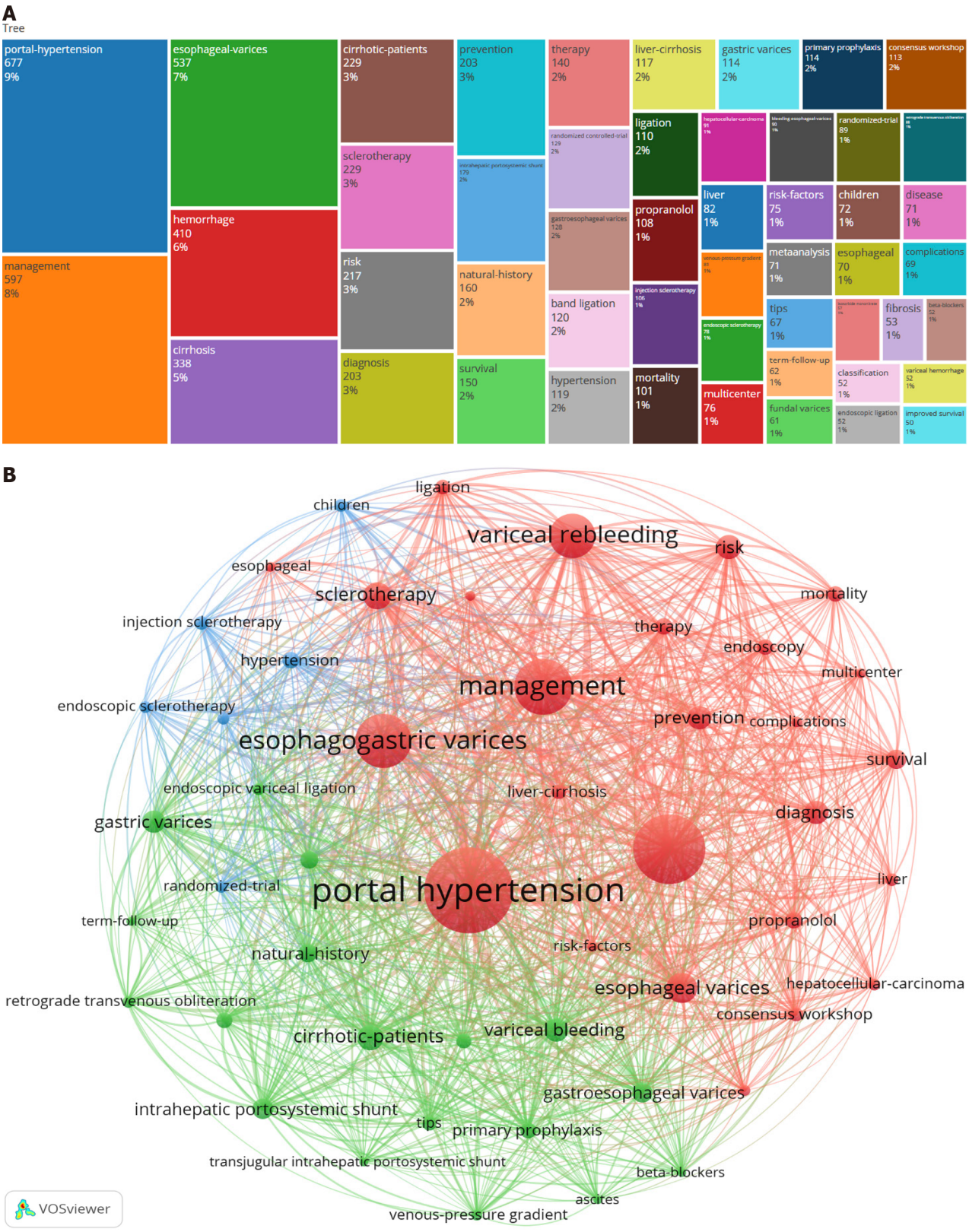


Figure 5 Esophagogastric variceal bleeding keyword analysis. A: Tree map of top 50 keywords; B: Clustering of top 50 keywords.

Burst keywords and research trends

The core keywords in EGVB include "portal hypertension", "management", "cirrhosis", "risk", "prevention", and "diagnosis". EGVB is a life-threatening complication of PH. Lesmana *et al*[30] conducted a thorough review on the development and management of PH and varices in cirrhotic patients, integrating international guidelines with real-world experiences from Indonesia. Several noninvasive and minimally invasive tools, including Doppler ultrasound, contrast-enhanced ultrasound, and TE, have been developed in clinical practice as alternatives to HVPG. However, despite having a certain degree of specificity, their sensitivity is not high, and some specific patients, such as those with

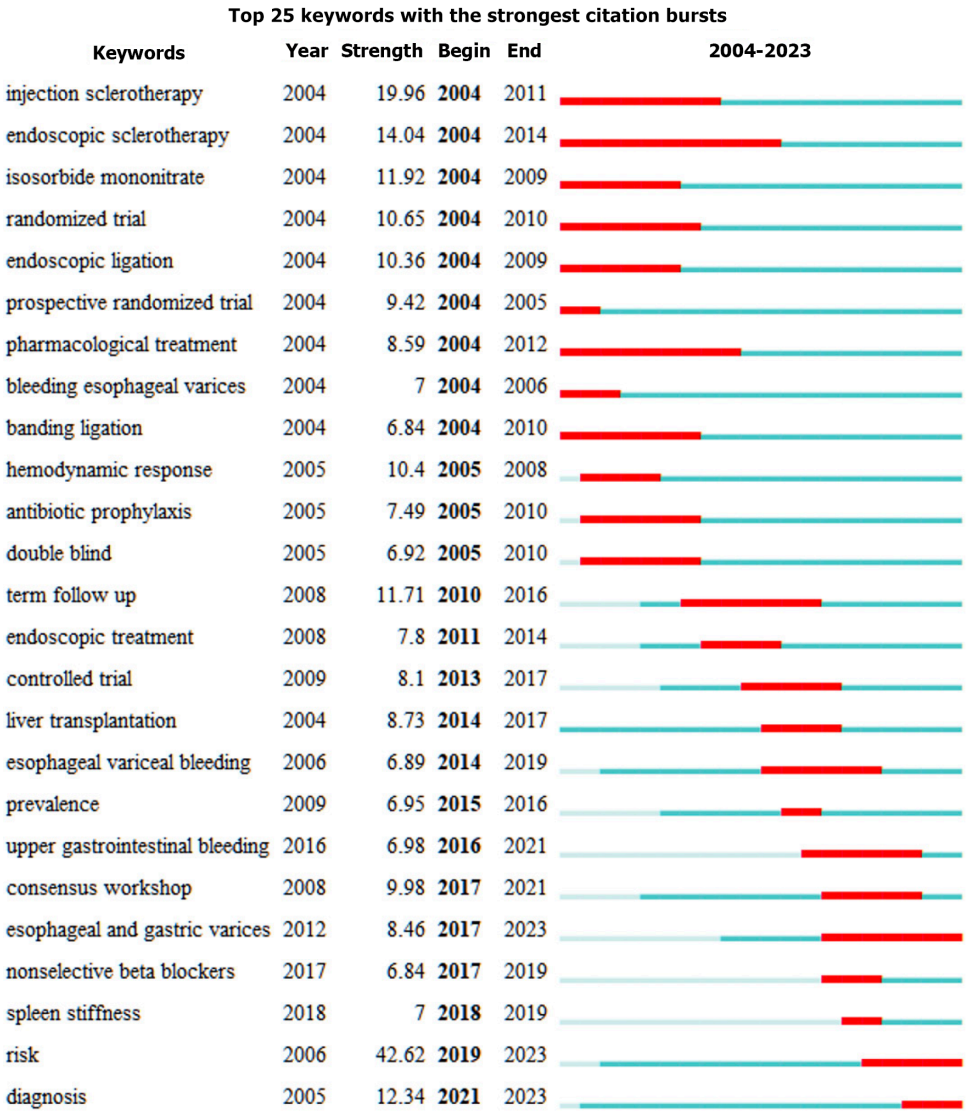


Figure 6 Top keywords with the highest occurrence bursts in esophagogastric variceal bleeding research.

obesity, have a high failure rate in measurements. TE is currently one of the most important noninvasive measurement methods. The Baveno VI consensus workshop recommends that an LSM with a TE ≥ 20-25 kPa, either alone or in combination with platelet count and spleen size, can be used to identify CSPH in patients with viral cirrhosis. Jindal *et al* [31] analyzed the clinical outcomes of patients with severe alcoholic hepatitis who developed acute-on-chronic liver failure. Although variceal bleeding and variceal severity are not associated with mortality, patients with an HVPG ≥ 20 mmHg have a significantly greater incidence of large varices and variceal bleeding[31]. Hagström *et al*[32] and colleagues conducted a cohort study in Sweden from 2006 to 2020 on 3592 patients who experienced their first episode of EGVB, focusing on the effectiveness of secondary prevention. The results revealed that secondary prevention measures were not widely implemented, with 65% of patients dying during the follow-up period. Patients who received standardized secondary prevention had better overall survival rates, highlighting the need to improve awareness of proper preventive strategies among clinicians and patients[32]. Additionally, PH in children is also worth attention. Alkhasov *et al*[33] used portosystemic shunt surgery to treat pediatric patients with hepatic PH, achieving good outcomes with all children, eliminating the risk of EVB. Unlike in adults, where PH is caused primarily by liver fibrosis and cirrhosis, PH in children is often due to PVT or congenital malformations[33]. Goel *et al*[34] utilized TE and von Willebrand factor antigen to predict PH and decompensation in children, which helps clinicians diagnose clinically significant varices while avoiding unnecessary invasive procedures.

The management of patients with EGVB is crucial for preventing bleeding. In 2023, the AASLD updated their 2017 guidelines on the management of PH and EGV. In addition to the previously mentioned content, the updated guidelines place special emphasis on the concept of compensated advanced chronic liver disease, noninvasive assessments of portal pressure, emerging drug options for PH, and its vascular etiology. The guidelines also suggest potential future guidance for managing pediatric PH[14]. Cheung *et al*[35] conducted a network meta-analysis comparing the effects of carvedilol and other NSBBs on variceal bleeding rates and mortality. The results indicated that while carvedilol was slightly less effective than nadolol in reducing variceal bleeding rates, it ranked highest in reducing all-cause mortality and had the lowest incidence of adverse effects, making it the preferred NSBB for treating varices[35]. Ryu *et al*[36] conducted a

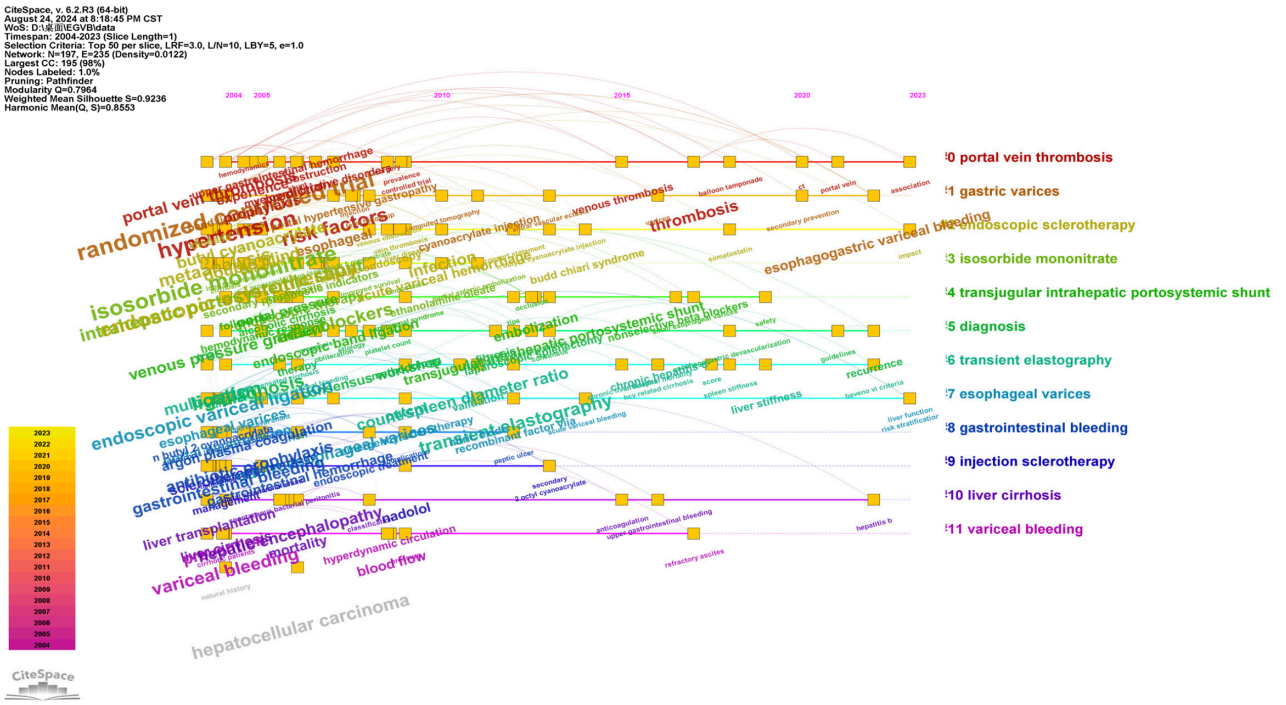


Figure 7 Timeline of keywords related to esophagogastric variceal bleeding.

retrospective analysis of 285 cirrhotic patients who underwent endoscopic variceal ligation (EVL). They discovered that EV with a larger diameter, as observed *via* CT, was associated with a greater risk of early bleeding following EVL treatment. Early identification of this high-risk group could allow for adjustments in treatment strategies, potentially improving patient outcomes[36]. Gan *et al*[37] evaluated the use of prophylactic antibiotics in patients with acute upper gastrointestinal bleeding. The results showed that prophylactic antibiotic use significantly reduced mortality in patients with variceal bleeding compared with those not treated with antibiotics, demonstrating clinical significance[37].

Liver cirrhosis is the leading cause of EGVB, as it increases portal vein pressure, forcing blood to seek alternative pathways. Fragile varices in the esophagus and gastric fundus are prone to rupture, and if bleeding occurs without timely intervention, it poses a life-threatening risk. In 2023, the Chinese Medical Association published the latest guidelines for the prevention and treatment of cirrhosis-related EGVB. These guidelines focus on a noninvasive diagnosis, screening for high-risk patients, primary and secondary prevention, and treatment of EGVB. The guidelines also highlighted several key issues and prospects in the field of cirrhosis-related EGVB. These include defining the concept and clinical indicators of cirrhosis recompensation and PH reversal, exploring whether relevant biomarkers can predict the risk of EGVB, and investigating the mechanisms of traditional Chinese medicine in antifibrosis and cirrhosis treatment[37]. Li *et al*[38] used the international normalized ratio (INR) and albumin-bilirubin to predict EGVB after endoscopic treatment in cirrhotic patients. Their model's albumin-bilirubin receiver operating characteristic curve and assessments at 1 month, 3 months, and 12 months demonstrated significant advantages over existing models, especially in predicting early rebleeding, which may be helpful for clinical diagnosis and treatment in the future[38]. For cirrhotic patients with refractory ascites, NSBB reduces the incidence of variceal bleeding but may impair cardiac function, potentially worsening ascites. Mingpun *et al*[39] conducted a retrospective study on this issue and demonstrated that maintaining a heart rate between 55 beats and 60 beats per minute in these patients is a safe approach for preventing variceal bleeding. Huang *et al*[40] evaluated the efficacy and safety of an emergency TIPS in cirrhotic patients with hepatocellular carcinoma (HCC) and AVB. Among 33 cirrhotic patients with HCC, one patient died from acute liver failure postoperatively, while the remaining patients did not experience rebleeding within five days. The 6-week and 1-year survival rates were 87% and 65%, respectively, suggesting that an emergency TIPS is both feasible and effective. Additionally, splenectomy can reduce portal pressure, decrease blood flow, improve hematologic parameters, and lower the risk of EGVB in cirrhotic patients with PH[40]. Wang *et al*[41] conducted a 10-year single-center follow-up study on the use of anticoagulants after laparoscopic splenectomy plus esophagogastric devascularization. The findings revealed that patients who received perioperative anticoagulant therapy had significantly lower rates of portal venous system thrombosis, rebleeding, and PVT formation than did those who did not receive anticoagulation therapy. These results were especially pronounced in women with a history of variceal bleeding, larger portal vein diameters, and slower portal venous flow[41].

Liver cirrhosis is an inevitable outcome in the progression of chronic liver disease to its end stage, with EGVB being a significant risk factor for cirrhosis-related complications and the leading cause of death in patients with cirrhosis and PH. Identifying the risk factors for EGVB is crucial for controlling the prognosis of patients with cirrhosis. The relationship between gastroesophageal reflux disease and cirrhosis has rarely been discussed, but some studies suggest that reflux esophagitis may be a risk factor for EGVB. Proton pump inhibitors (PPIs) have been widely used to reduce the risk of EGVB in cirrhotic patients. Increased gastric pressure and the frequency of transient lower esophageal sphincter relaxation are considered key factors contributing to gastroesophageal reflux disease in cirrhotic patients[42]. Yardeni *et al*

[43] investigated the prevalence of CSPH in patients with chronic liver disease. In their study of 326 patients, those with metabolic dysfunction-associated steatotic liver disease had a higher rate of EVB than patients with viral liver disease, alcoholic liver disease, or both, despite having significantly lower MELD-Na scores. These findings suggest that the MELD-Na score may underestimate the severity and bleeding risk in metabolic dysfunction-associated steatotic liver disease patients[43]. A multicenter international study evaluated whether first-line treatment with lenvatinib in patients with advanced HCC increases the risk of EGVB. A total of 535 patients from 12 centers across Italy, Korea, and Japan participated. The results revealed that while the overall risk of EGVB was low in HCC patients treated with lenvatinib, the risk was significantly greater in those with high-risk EV at baseline[44].

Prevention has always been a primary focus for hepatologists and researchers. Research on noninvasive risk stratification tools (primarily prediction models), pharmacological treatments, endoscopic treatments, surgical interventions, imaging techniques, metabolomics, and combination therapies remains at the forefront of the EGVB field. Among the risk stratification tools, the Baveno VII criteria are the most prominent, but they are primarily designed to predict variceal risk in cirrhotic patients; however, their applicability in patients with advanced HCC has not yet been validated[45-47]. Wu *et al*[48] successfully validated the Baveno VII criteria as a safe and accurate model for predicting high-risk varices and liver-related events in patients with HCC. The rate of missed varices requiring treatment was 3.5%, and a 5% missed diagnosis rate was deemed acceptable when alternative LSM and platelet thresholds were considered. Noninvasive prevention of EGVB in the advanced HCC population may become a critical focus moving forward[48]. Wang *et al*[49] identified EGVB in cirrhotic patients *via* the liver stiffness-spleen diameter-to-platelet ratio (LSPS) model and applied this model for risk stratification in the secondary prevention of EGVB. The results showed that LSPS-based stratification is a reliable noninvasive method that effectively detects high-risk events in the secondary prevention of EGVB[49]. Research related to CT and shear wave elastography has been considered a potential noninvasive measurement for PH, with potential predictive value for cirrhosis-related EGVB[50-53]. CSPH is considered a key milestone in the progression of cirrhosis. Previous studies have suggested that visceral volume measurements may serve as a predictive tool for the development of PH. Romero-Cristóbal *et al*[54] applied multidetector computerized tomography to predict CSPH in HCC patients, followed by HVPG assessments. The results indicated that quantifying liver and spleen volume could accurately predict PH. Whether this research can be expanded for broader application remains to be determined[54].

PH is the primary driving factor for decompensated cirrhosis. Carvedilol, a newer NSBB, is more effective at reducing portal pressure due to its additional α-blocking properties; it also has antioxidant, anti-inflammatory, and antifibrotic properties. Carvedilol, the preferred drug for EGVB prevention according to the Baveno VII guidelines, is recommended for both primary and secondary prevention of EGVB. Compared with EVL, carvedilol is more effective in the primary prevention of EGVB. Compared with propranolol, another NSBB, carvedilol reduces the risk of liver decompensation through a greater hemodynamic response rate. For secondary prevention, the combination of EVL and carvedilol has better efficacy than EVL or propranolol alone[55]. In terms of safety, carvedilol is safe for patients with ascites and EGVB, and maintaining adequate arterial blood pressure can improve survival rates. Increasing evidence suggests that carvedilol may delay decompensation and improve survival in patients with advanced cirrhosis and refractory ascites. As a result, a broader range of patients with advanced chronic liver disease should be considered in the future[56]. PPIs are widely used to treat various digestive system diseases related to excess stomach acid. However, there is still controversy regarding the occurrence of complications, particularly gastrointestinal bleeding, after EVT. Zhang *et al*[57] investigated the effects of PPIs use on complications in cirrhotic patients, including 143 patients during hospitalization after endoscopic variceal treatment (EVT). The results revealed that the incidence rates of gastrointestinal bleeding and other post-EVT complications were 4.90% and 46.85%, respectively. PPIs use did not significantly reduce the risk of complications; therefore, PPIs are not recommended for preventing complications during hospitalization after EVT[57].

Endoscopic treatment is the first-line emergency method for EGVB and plays a critical role in reducing mortality from acute bleeding and preventing rebleeding. Compared with pharmacological or surgical interventions, endoscopic techniques have a higher hemostasis rate and a lower risk of complications. The main treatment methods include EVL, endoscopic band ligation (EBL), endoscopic injection sclerotherapy (EIS), and gastroscopic tissue adhesive injection. These techniques effectively control bleeding and prevent recurrence by cutting off blood flow or rapidly coagulating the blood. Wei *et al*[58] conducted a multicenter randomized controlled trial in cirrhotic patients with AVB and hypersplenism comparing partial splenic embolization combined with endoscopic treatment *vs* endoscopic treatment alone. The results demonstrated that the 5-year rebleeding and variceal recurrence rates in the combined treatment group were significantly lower than those in the endoscopic-only group. Combined treatment was identified as the sole independent risk factor influencing outcomes and improved peripheral blood counts and liver function[58]. Lv *et al*[59] examined whether nonmalignant PVT affects outcomes in cirrhotic patients with AVB, a topic not addressed in the Baveno VII consensus. Multiple models adjusted for confounding factors to assess the impact of PVT on clinical outcomes. The results revealed no direct evidence that PVT influences prognosis, either positively or negatively, in cirrhotic AVB patients receiving standard treatment[59]. Zhang *et al*[60] analyzed the safety and efficacy of endoscopic submucosal dissection for cirrhotic patients with early-stage cancer or precancerous lesions in the upper gastrointestinal tract *via* data from a 10-year cohort at major Chinese medical institutions. No patients experienced liver function deterioration after completing treatment, and neither endoscopic submucosal dissection, liver function impairment, nor gastrointestinal tumors themselves caused death, with severe adverse events being rare[60]. Taki *et al*[61] reviewed the effects of EIS and balloon-occluded retrograde transvenous obliteration in the secondary prevention of gastric variceal bleeding and their impact on liver function. The results demonstrated that EIS is an effective treatment method, with no significant changes in liver function after treatment[61]. One research team evaluated the safety of EBL in cirrhotic patients with platelet counts < 50 g/L or INRs ≥ 1.5. They reported that the incidence of procedure-related bleeding within 30 days post-EBL was less than 2.6%. High MELD scores, particularly elevated bilirubin levels, were found to be significantly associated with an increased risk of variceal bleeding following EBL[62].

TIPS is an interventional technique used to manage complications of PH. By creating a channel between the portal vein and the hepatic vein within the liver, TIPS effectively reduces pressure in the portal venous system. This procedure is widely used in conditions caused by PH, such as cirrhosis, and is typically recommended for secondary prevention of EGVB when standard treatments fail. Li *et al*[63] assessed the safety and efficacy of emergency TIPS as a first-line treatment for cirrhotic patients with acute EGVB. The study reported a 100% success rate for TIPS procedures, with all patients transferred to general wards after surgery. No rebleeding occurred within five days, and the rebleeding rates at six weeks and two years were 6.6% and 1.3%, respectively. The transplant-free survival rates at six weeks, one year, and two years were 94.7%, 93.4%, and 84.6%, respectively. Major complications, including acute liver failure, hepatic encephalopathy, and shunt dysfunction, occurred at rates of 5.3%, 25%, and 5.3%, respectively. Overall, TIPS is a highly effective and safe treatment option for patients with advanced cirrhosis and acute EGVB, offering a stable management strategy, particularly in centers lacking immediate access to emergency endoscopy[63]. Mukund *et al*[64] demonstrated that performing emergency TIPS within eight hours significantly improved survival rates in patients with refractory variceal bleeding, underscoring the critical importance of timely intervention in TIPS therapy. However, for high-risk patients prone to rebleeding, there are currently no specific guidelines for treating those with HCC and symptomatic PH[64]. Chen *et al*[65] investigated patients with PH and HCC who had failed standard treatments and compared the efficacy of TIPS *vs* endoscopy combined with NSBB in preventing rebleeding. Their findings revealed that TIPS not only significantly reduced rebleeding rates but also improved adherence to targeted therapies for HCC and extended overall survival[65]. Studies comparing TIPS and endoscopy plus NSBB standard treatments for variceal bleeding patients have shown that when the HVPG is greater than 16 mmHg, TIPS can significantly improve transplant-free survival rates[66]. Wu *et al*[67] compared balloon-compression endoscopic injection sclerotherapy(bc-EIS) with TIPS for treating rebleeding after EVL and reported that the incidence of hepatic encephalopathy and total bilirubin levels were lower in the bc-EIS group than in the TIPS group, with no significant difference in rebleeding rates; this suggests that bc-EIS could be a suitable alternative for medical centers unable to perform TIPS[67].

Metabolomics, following genomics and proteomics, is an emerging field that studies the changes in metabolites or the variations in metabolite levels over time in biological systems (cells, tissues, or organisms) after they have been stimulated or disturbed. Metabolomics offers a powerful means to investigate biological systems by analyzing metabolic changes under disease conditions, thereby aiding in the identification of potential biomarkers for early diagnosis. Ai *et al*[68] utilized serum metabolomics based on ultra-performance liquid chromatography coupled with tandem mass spectrometry to screen for specific biomarkers of EGVB-specifically citrulline and alpha-aminobutyric acid-in a discovery cohort. These biomarkers were subsequently validated in two independent validation cohorts[68].

AI technologies and machine learning methods have also been widely applied in the field of EGVB, particularly in the identification, prediction, and management of the disease. In addition to the previously mentioned ENDOANGEL-GEV AI system, which segments and classifies gastroesophageal varices *via* six models, deep learning-based techniques have been employed to automatically measure the spleen volume from CT images. These findings provide new indicators for detecting high-risk varices in patients with compensated hepatitis B cirrhosis[69]. A novel machine learning-driven radiomic model was developed to identify patients with EV at high risk of bleeding. The study included 796 eligible participants, including patients with EV at low- and high-bleeding-risk. The model demonstrated a high AUROC value of 0.983 and exhibited good sensitivity and specificity in internal validation[70]. Additionally, advancements in endoscopic treatment technologies and standardized nursing measures have significantly improved the efficacy of upper gastrointestinal bleeding management. New hemostatic techniques, such as over-the-scope clips and hemostatic powders, have shown potential in treating refractory cases[71].

In economically developed countries with abundant medical resources, newer technologies and treatment options may help reduce health care costs and alleviate the financial burden on patients. In contrast, in developing countries, the lack of medical resources and preventive measures directly affects the cost-effectiveness of liver disease treatments and disease control outcomes. In Spain, Bañares *et al*[72] evaluated the cost-effectiveness of TIPS in treating EGVB and refractory ascites, tracking treatment costs and unrelated adverse events over a two-year period. The study indicated that TIPS may be a cost-effective and cost-saving alternative to standard therapies[72]. A cross-sectional study from Ethiopia on chronic liver disease patients revealed that higher-grade varices, a lack of NSBB use, infections, thrombocytopenia, and age were associated with higher bleeding rates, most of which are preventable factors[73]. Additionally, PH caused by NCPH deserves attention, such as in cases of polycythemia vera (PV). Previously considered a separate disease from NCPH, some case reports have shown that PV patients present with moderate to severe EV, PVT, and splenomegaly, while liver function remains relatively preserved. PV patients are recommended to undergo early esophagogastroduodenoscopy screening, and primary preventive measures should be taken if necessary[74].

CONCLUSION

In summary, EGVB is a common and severe complication in patients with liver cirrhosis. In recent years, significant progress has been made in areas such as risk assessment, early diagnosis, and personalized treatment. The development of non-invasive diagnostic techniques, such as the widespread application of TE, along with treatment methods based on individualized risk stratification, has markedly improved the prevention and management of EGVB. However, despite these advancements, several key issues remain unresolved, necessitating further research and exploration. In the future, research on EGVB should focus on the following key directions to address current challenges and advance clinical practice:

Development of new treatment strategies

Building on existing research findings, explore novel treatment methods for EGVB to enhance therapeutic outcomes and improve patients' quality of life. This includes identifying new drug targets and developing comprehensive treatment plans that combine endoscopic surgery with TIPS.

Utilizing AI for risk prediction and personalized medicine

Incorporating AI and machine learning technologies can more accurately predict the bleeding risk of EGVB and formulate personalized treatment plans, achieving precision medicine. This will aid in risk stratification and bleeding prevention, further reducing recurrence and complications.

Exploring the role of gut microbiota in EGVB

In recent years, the importance of gut microbiota in various diseases has become increasingly evident. Future research should focus on the specific roles of gut microbiota in the pathogenesis of EGVB to identify potential intervention targets and provide new treatment avenues.

Optimizing non-invasive detection techniques

Further enhance the sensitivity and accuracy of diagnostic tools such as TE, particularly in non-invasive risk stratification models. For example, studies based on LSM with platelet count (LSPS) have shown great potential in secondary prevention. Continued development of such models will aid in early screening and risk assessment.

Multidisciplinary collaboration and standardization

Standardizing multidisciplinary collaborative treatments is imperative. Clinicians should place greater emphasis on interdisciplinary cooperation, integrating new technologies such as imaging and metabolomics to achieve breakthroughs in early screening and personalized treatment. This will promote the optimization of diagnostic methods and the innovation of treatment strategies.

Long-term follow-up studies

Conduct long-term follow-up studies to evaluate the prognosis and sustained treatment efficacy in EGVB patients, providing more comprehensive evidence for clinical decision-making. This will help in understanding the long-term impacts of different treatment methods and optimizing treatment protocols.

Multicenter collaborative research

Through cross-institutional collaboration, increase sample sizes and the scope of studies to enhance the generalizability and credibility of research findings. This is crucial for validating new discoveries and promoting effective treatment strategies. In conclusion, with the continuous integration of cutting-edge technologies and clinical practice, research in the EGVB field will achieve greater progress in optimizing diagnostic methods, personalized treatment, and multidisciplinary collaboration. We anticipate witnessing more groundbreaking developments that will provide safer and more effective treatment options for EGVB patients worldwide.

FOOTNOTES

Author contributions: Wang DX conceived and designed the study; Wang DX and Wu XJ participated in data processing and statistical analysis, and drafted the manuscript, they contributed equally to this article, they are the co-first authors of this manuscript; Yu JZ, Zhan JY, Xing FF contributed to data analysis and interpretation; Liu W, Chen JM, Liu P, Liu CH, Mu YP supervised the review of the study; Liu CH, Mu YP they contributed equally to this article, they are the co-corresponding authors of this manuscript; and all authors seriously revised and approved the final manuscript.

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CASE REPORT

Multimodal diagnostic and surgical approach to spontaneous esophageal rupture induced by severe coughing: A case report

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Abstract

BACKGROUND

Boerhaave syndrome, or spontaneous esophageal rupture, is a rare and life-threatening emergency, typically caused by a sudden increase in esophageal pressure due to violent coughing or vomiting. Early diagnosis is challenging as its symptoms often resemble those of other diseases. Understanding its pathological features and treatment strategies is therefore critical for clinical practice.

CASE SUMMARY

This report describes a case of spontaneous esophageal rupture triggered by violent coughing in a 55-year-old male with a history of smoking and hypertension. Following severe coughing, the patient developed chest pain, vomiting, and respiratory distress. Initial clinical evaluation was inconclusive, with a suspected diagnosis of cardiovascular or gastrointestinal conditions. After further examination, the diagnosis of spontaneous esophageal rupture was confirmed. Chest X-ray, computed tomography, and endoscopy revealed a rupture in the lower esophagus, along with mediastinal abscess and pleural effusion. Laboratory tests showed mild infection markers. The patient underwent surgical repair of the esophageal rupture (approximately 3 cm in length) with mediastinal drainage. Postoperatively, the patient's temperature normalized within 3 days, respiratory function improved, and pleural effusion significantly decreased. After two weeks of treatment, the patient was discharged without complications and had a favorable prognosis. The study suggests that while violent coughing is a rare trigger, it can lead to severe damage, and imaging techniques play a crucial role in diagnosis.

CONCLUSION
Spontaneous esophageal rupture presents significant diagnostic and therapeutic challenges. Early recognition and timely intervention are crucial for improving prognosis. This case highlights the importance of imaging and surgical treatment, offering new insights for managing similar cases and providing valuable clinical guidance.

Key Words: Esophageal rupture; Spontaneous; Boerhaave syndrome; Cough; Severe; Surgical treatment; Diagnosis; Differential; Case report

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Core Tip: This study thoroughly reveals the pathology of spontaneous esophageal rupture induced by severe coughing. It systematically documents the complete diagnostic and treatment process of esophageal rupture for the first time. Advanced imaging techniques are employed to accurately locate esophageal injuries. A personalized surgical strategy is implemented, significantly improving treatment success rates. The findings offer innovative strategies for managing similar rare cases.

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INTRODUCTION

The esophagus is a crucial component of the digestive system, primarily responsible for transporting food from the mouth to the stomach. The health of the esophagus is directly linked to the digestive process and overall quality of life[1]. Esophageal diseases include esophagitis, esophageal cancer, foreign bodies in the esophagus, and esophageal rupture[2]. Among these, spontaneous esophageal rupture, also known as Boerhaave syndrome, is rare but considered a medical emergency due to its high mortality rate and severe complications[3]. This condition typically results from the sudden rupture of the esophageal wall, leading to severe pain and other life-threatening symptoms. A thorough understanding of its pathophysiology, diagnostic methods, and treatment strategies is crucial for improving patient survival rates[4].

Recent studies indicate that the mortality rate for spontaneous esophageal rupture is extremely high, particularly when there is a delay in diagnosis and treatment[5-7]. The urgency of the condition arises from the fact that once the esophagus ruptures, food, gastric acid, and saliva can enter the thoracic cavity, causing serious infections and inflammation, such as suppurative pleuritis. Therefore, prompt and accurate diagnosis is critical for effective treatment and prognosis. Spontaneous esophageal rupture is challenging to diagnose due to its diverse and nonspecific clinical manifestations, often leading to misdiagnosis as other chest or abdominal conditions. Diseases such as esophagitis, esophageal cancer, acute myocardial infarction, and gastroesophageal reflux disease share similar symptoms (*e.g.*, chest pain, difficulty breathing). However, diagnosis requires thorough history taking, clinical assessment, and imaging studies [such as computed tomography (CT) scans or endoscopy]. Early and accurate diagnosis is especially critical in the absence of typical triggers, such as severe vomiting or coughing. Therefore, when faced with similar symptoms, heightened awareness and prompt diagnostic measures are essential[8-10].

Literature reports indicate that spontaneous esophageal rupture can be caused by severe vomiting, overeating, or direct trauma and may present with symptoms such as severe chest pain, dyspnea, and subcutaneous emphysema[11-13]. Treatment typically involves emergency surgery and the placement of a chest tube to prevent or manage infection [14]. Although esophageal rupture due to severe coughing is rarely reported, this suggests that there are still many unexplored and poorly understood areas in this field.

Despite the increasing number of studies and case reports on spontaneous esophageal rupture, existing literature primarily focuses on the general characteristics of the disease, with insufficient in-depth analysis and discussion of cases caused by specific factors. Current diagnostic criteria, treatment protocols, and patient management strategies for this condition remain inadequate, underscoring the need for further research to fill these knowledge gaps, particularly through detailed documentation and analysis of cases caused by specific triggers. Such research is essential to improve the diagnosis and treatment of these cases[15].

This study reports a case of spontaneous esophageal rupture induced by severe coughing, providing empirical data aimed at improving diagnostic and treatment strategies, as well as increasing healthcare professionals' awareness of such cases. By enhancing early diagnosis and individualized treatment, the study aims to reduce mortality associated with this condition and improve patients' quality of life.

CASE PRESENTATION

Chief complaints

The patient was conscious and reported severe pain in the aforementioned areas, accompanied by significant difficulty breathing.

History of present illness

This paper reports on a 59-year-old male patient who presented to Guangzhou Traditional Chinese Medicine Hospital on December 18, 2023, with severe pain in the left side of his back, chest, and upper abdomen following a severe coughing episode that occurred six hours prior.

History of past illness

No similar symptoms in the past, no significant medical history, denies smoking and alcohol consumption.

Personal and family history

The patient maintains a regular lifestyle, has no family history of chronic diseases, and has not been exposed to harmful environments or chemicals.

Physical examination

Upon arrival at the hospital, the patient's vital signs were as follows: Blood pressure of 145/85 mmHg, heart rate of 110 beats *per* minute, respiratory rate of 22 breaths *per* minute, body temperature of 37.5 °C, and oxygen saturation of 92%.

Imaging examinations

The initial imaging assessment, including a contrast-enhanced CT scan of the chest and abdomen (Figure 1A), revealed a small left-sided pneumothorax, approximately 30% compression of lung tissue, minor mediastinal emphysema, and signs of emphysema and bullae formation in both upper lungs. The preliminary diagnosis was esophageal rupture. Subsequently, a diagnostic thoracentesis was performed under ultrasound guidance (Figure 2), extracting dark, turbid fluid containing small esophageal debris. A chest tube was then inserted, draining approximately 700 mL of dark digestive fluid, accompanied by gastrointestinal decompression. An esophagogram (barium swallow test) revealed contrast leakage from the lower esophagus into the thoracic cavity (Figure 3A).

FINAL DIAGNOSIS

Based on the clinical presentation and auxiliary examination results, a final diagnosis of spontaneous esophageal rupture was confirmed.

TREATMENT

Upon admission, the patient immediately received emergency management, including oxygen therapy to alleviate respiratory distress, analgesics to reduce pain, fasting, and gastrointestinal decompression to relieve gastrointestinal pressure. The patient underwent emergency esophageal repair surgery under general anesthesia. Preoperative evaluations included esophageal contrast radiography, chest CT, blood tests, and an electrocardiogram, which confirmed the location and size of the perforation in the lower esophagus. Prophylactic intravenous antibiotics were administered, and the anesthesia team performed a preoperative assessment, ultimately opting for general anesthesia.

The diagnosis was initially confirmed through esophageal contrast radiography and chest CT, which clarified the location and size of the esophageal rupture. Surgery was performed *via* a left thoracotomy, approximately 20 cm in length, selected for optimal surgical access. The procedure began with the removal of gastric contents and purulent material from the thoracic cavity, followed by thorough debridement. Gastroscopy was used to precisely locate the esophageal perforation, which was found above the diaphragm with a rupture measuring approximately 2.5 cm. A double-layer repair was performed using absorbable sutures, and a water test confirmed the absence of leaks at the anastomosis. The thoracic cavity was repeatedly irrigated postoperatively, with further reinforcement of the repair as needed. Postoperative gastroscopy confirmed a well-healed anastomosis, and a duodenal feeding tube was inserted.

OUTCOME AND FOLLOW-UP

The patient was transferred to the intensive care unit for close monitoring. Postoperative esophageal contrast radiography and chest/abdominal CT confirmed the success of the repair. A chest drainage tube was placed within 24 hours to drain accumulated fluid, and was removed after 72 hours based on imaging results. Pain management was provided through a fentanyl pump, initially set at 1 mcg/hour and adjustable up to 2 mcg/hour, with continuous administration for 3 days. Antimicrobial therapy included imipenem (0.5 g IV every 6-8 hours for 10 days) and

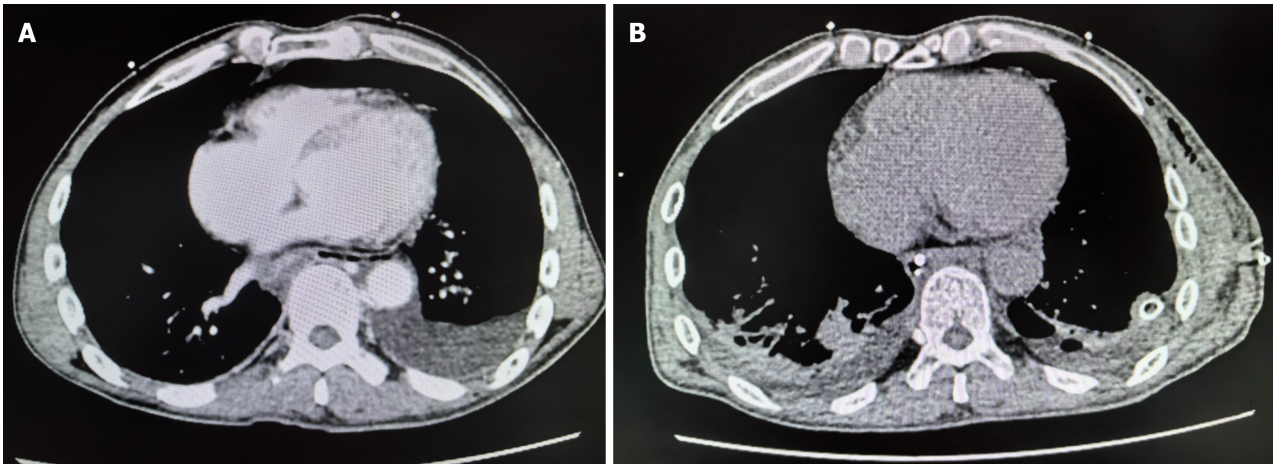


Figure 1 Computed tomography scans. A: Initial chest and abdominal computed tomography (CT) scans of the patient. CT results indicate a small left-sided pneumothorax caused by severe coughing; approximately 30% compression of the lung tissue is observed; B: Postoperative CT scan. The follow-up CT scan shows a reduction in the left-sided pneumothorax and significant absorption of the mediastinal emphysema, suggesting marked improvement in the thoracic condition.



Figure 2 Ultrasound-guided thoracentesis. Diagnostic thoracentesis was performed under ultrasound guidance, yielding dark brown turbid fluid containing esophageal debris.

metronidazole (500 mg IV every 8 hours for 10 days). Pancreatic secretion suppression was achieved with octreotide (0.1 mg subcutaneously every 8 hours for 6 days) and somatostatin (3-6 mg/hour continuous IV infusion for 60 hours). Omeprazole was administered for gastric protection. The patient was transitioned to a semi-liquid diet to reduce esophageal strain and support nutritional recovery. Laboratory results showed improvement in inflammatory markers (C-reactive protein, procalcitonin, total protein, and albumin).

During the follow-up period, imaging examinations indicated that the patient was recovering well. A follow-up CT scan on December 25, 2023, showed a significant reduction in the left-sided pneumothorax (Figure 1B). An esophagogram conducted on December 26, 2023, revealed no leakage of contrast material (Figure 3B). A chest digital radiography panoramic scan on December 29, 2023, demonstrated improvement in the left-sided hydropneumothorax and bilateral lower lung infiltration. On the same day, the chest tube was removed, and the patient was transitioned to a semi-liquid diet. The patient was successfully discharged on January 1, 2024, with plans for regular follow-up observations.

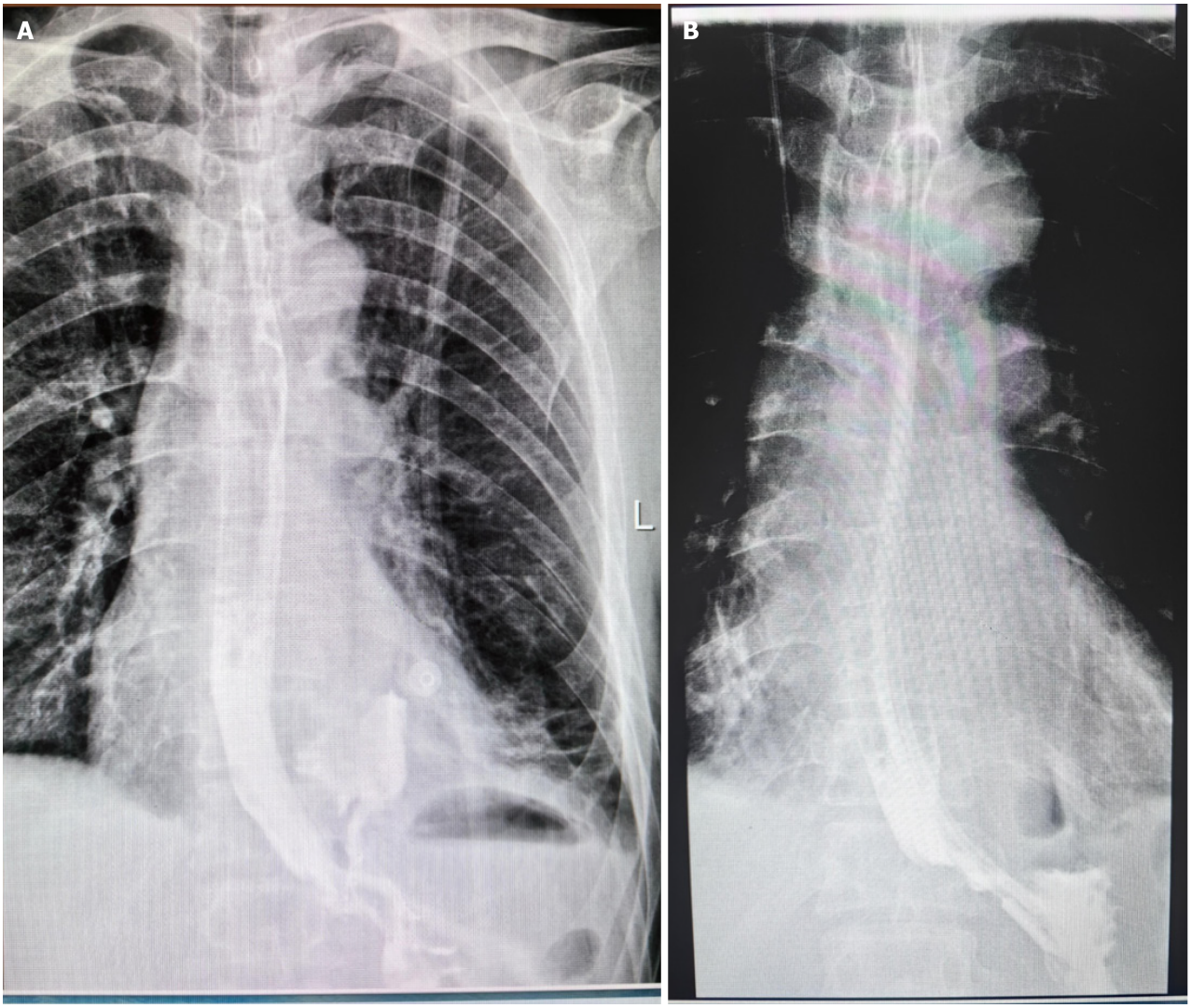


Figure 3 Esophagogram. A: The esophagogram reveals contrast leakage into the thoracic cavity from the lower esophagus, indicating an esophageal rupture; B: Postoperative esophagogram review. The postoperative esophagogram revealed no contrast leakage, indicating the successful repair of the esophageal perforation.

DISCUSSION

Overview

Spontaneous esophageal rupture, also known as Boerhaave syndrome, is a rare and life-threatening medical emergency. This condition is typically triggered by severe vomiting or coughing, although it can occasionally be caused by dysphagia or the ingestion of large objects. Esophageal motility disorders, excessive alcohol consumption, and certain eating disorders may increase esophageal pressure, thereby elevating the risk of rupture[16]. The rarity and nonspecific clinical presentation of spontaneous esophageal rupture make its diagnosis particularly challenging, often leading to misdiagnosis as other thoracic emergencies. Initial diagnosis generally relies on chest X-rays and CT scans, with contrast esophagography being the diagnostic gold standard[17]. However, the diagnosis is frequently delayed due to the varied clinical manifestations of the condition. It is crucial to maintain a high index of suspicion, especially in patients presenting with acute chest pain following severe vomiting or coughing[18].

The treatment strategy is determined based on the patient's condition, the size and location of the rupture, and the presence of any infection. Treatment options range from conservative approaches, such as fasting, intravenous fluids, and antibiotic therapy, to more invasive procedures like primary repair, esophageal stent placement, or, in severe cases, esophagectomy[19]. The prognosis is highly dependent on the timeliness of diagnosis and treatment; early diagnosis and intervention are crucial for survival, while delays are associated with increased morbidity and mortality[20].

When selecting diagnostic tools, while various imaging techniques each have their strengths and limitations, CT scanning is preferred due to its high resolution and ability to rapidly provide critical information for decision-making. Although chest X-rays are cost-effective, they have lower resolution; magnetic resonance imaging offers better soft tissue contrast but requires longer scanning times; ultrasound is radiation-free and suitable for bedside use but is dependent on operator experience for detecting deep-seated lesions; nuclear medicine scans provide functional and metabolic information but are expensive and time-consuming. CT scanning can quickly and accurately identify the size and location of pneumothorax and detect other lung abnormalities, excelling particularly in bubble analysis. Enhanced CT also clearly

delineates blood supply to tissues and vessels, aiding in the identification of concomitant vascular lesions. These advantages make CT an ideal choice in emergency settings, enabling prompt and accurate diagnosis, which in turn facilitates quicker treatment decisions and improves patient outcomes (Supplementary Table 1).

Literature case review

We conducted a literature review using the search terms "Spontaneous Esophageal Rupture" and "Coughing" in the PubMed database, analyzing six representative studies from 1963 to 2024. Table 1 summarizes the clinical presentations, diagnostic methods, treatment options, and prognoses of the patients in these studies.

Aga *et al*'s study emphasizes the need for heightened awareness of spontaneous esophageal rupture, even in the absence of typical symptoms (*e.g.*, vomiting or severe coughing)[14]. Although their research focused on swallowing disorders as the primary trigger, our case suggests that severe coughing, as an atypical trigger, can also lead to esophageal rupture, expanding the range of potential causes. Thus, our findings challenge traditional views on esophageal rupture triggers and suggest a broader spectrum of factors should be considered in diagnosis. Sakatoku *et al*'s study highlights the importance of individualized treatment, presenting both conservative and surgical approaches[15]. Our case supports the effectiveness of conservative treatment in the absence of major complications but emphasizes the significant role of severe coughing as a trigger, offering a new perspective on early diagnosis and personalized treatment. However, Sakatoku *et al*[15] did not explore the impact of atypical triggers on treatment decisions, a gap our study addresses. Rajic and Schandl[19] cautioned that esophageal rupture may be confused with other chest conditions, such as pneumothorax or subcutaneous emphysema, complicating diagnosis. Our case faced similar challenges, particularly in the absence of typical triggers, underscoring the key role of imaging in excluding esophageal rupture. Although previous literature touches on this issue, there is a lack of specific guidance on improving diagnostic accuracy in atypical cases. Stevens *et al*[20] expanded the scope of esophageal rupture triggers, noting that vomiting could cause tracheal rupture in children. Similarly, our study suggests that severe coughing can also be a trigger, further supporting the wide range of potential causes for esophageal rupture. While Stevens *et al*[20] focused on vomiting, our research highlights the risk of coughing, emphasizing the importance of multiple triggers in esophageal rupture. Canelas Mendes *et al*[16] explored the atypical presentation of esophageal rupture in elderly patients, emphasizing the risk of misdiagnosis. Our study further corroborates this, particularly in cases with atypical histories and symptoms, where careful consideration is necessary. Bakhos *et al*[18] considered mediastinal emphysema typically benign did not require excessive intervention. However, our study suggests that mediastinal emphysema could be an early sign of esophageal rupture, warranting increased vigilance. Compared to Bakhos *et al*[18], our research advocates for further investigation into the possibility of esophageal rupture in similar cases.

In conclusion, this study reports a case of spontaneous esophageal rupture triggered by severe coughing, challenging the traditional view that only vomiting is a primary cause and expanding the spectrum of potential triggers. While the literature has primarily focused on typical triggers, our study underscores the importance of maintaining heightened awareness of atypical presentations, especially in the absence of clear triggers.

Regarding diagnosis, the symptoms of esophageal rupture are often nonspecific, such as chest pain, difficulty breathing, and subcutaneous emphysema, which can also be seen in other chest conditions. Existing literature highlights the risk of misdiagnosis, potentially delaying treatment and increasing patient risk (*e.g.*, Rajic and Schandl[19], Stevens *et al*[20]). Therefore, physicians should prioritize detailed history-taking, physical examination, and imaging to rule out esophageal rupture in cases with nonspecific symptoms.

In terms of treatment, conservative therapy, endoscopic stenting, and surgery each have their own advantages and limitations. Individualized treatment is critical, especially for patients with early diagnosis and no significant complications, where conservative management may suffice, while surgical intervention is necessary for extensive ruptures or severe complications. Sakatoku *et al*'s study also supports this, stressing that treatment plans should be adjusted based on the patient's specific condition[15].

Furthermore, the research by Cornejo *et al*[21] demonstrates the application of endoscopic and laparoscopic techniques, while Doğuç *et al*[22] explores the potential of artificial intelligence in early diagnosis. These technological advancements offer new possibilities for early diagnosis and treatment of esophageal rupture, suggesting that future research may benefit from these emerging technologies.

Critical analysis and study limitations

This study reports a case of spontaneous esophageal rupture induced by severe coughing, providing preliminary insights into the diverse causes of this condition. However, because the study is based on a single case, the generalizability of the findings is limited, making it difficult to apply them to all similar situations. Specifically, the selection of this case and individual differences may affect the reliability and applicability of the conclusions, potentially introducing bias in understanding the pathological features and treatment responses of other patient populations.

Although the study offers a relatively comprehensive analysis through imaging and clinical evaluation, its single-center design and small sample size may not capture the full variability of the disease. This limitation reduces the external validity of the results, making it challenging to fully reflect the diverse clinical presentations and treatment needs of spontaneous esophageal rupture. Therefore, future research should involve multi-center, large-scale studies to validate these findings and improve the reliability and generalizability of the results.

Moreover, while existing research provides some preliminary understanding of the pathological mechanisms, the lack of systematic studies on the underlying mechanisms means the pathophysiological processes of the disease remain unclear. Future studies should focus on more in-depth experimental and clinical research to better define the mechanisms of spontaneous esophageal rupture, providing a stronger theoretical foundation for more accurate diagnosis and treatment.

Table 1 Literature review on spontaneous esophageal rupture: Focus on cough-induced cases and their clinical outcomes

Journal	Ref.	PMID	Year	Case presentation	Diagnosis	Treatment	Outcome
Case Rep Emerg Med	Aga *et al*[14]	26949552	2016	Esophageal rupture after swallowing a chicken nugget	CT scan	IV fluids, antibiotics, esophageal stent, VATS drainage	Unspecified
Nagoya J Med Sci	Sakatoku *et al*[15]	31849387	2019	Thoracic empyema after spontaneous esophageal rupture, recurrent episodes	CT, Endoscopy	Conservative therapy, subtotal esophagectomy	Resolved, no recurrence
Radiol Case Rep	Rajic and Schandl[19]	35345564	2022	Pneumomediastinum after masturbation, not directly related to esophageal rupture but relevant for differential diagnosis	Clinical observation	Not applicable	Not applicable
Am J Otolaryngol	Stevens *et al* [20]	20015755	2010	Tracheal rupture by vomiting, highlights diagnostic considerations similar to esophageal rupture	CT scan	Conservative management	Resolved
Cureus	Canelas Mendes *et al* [16]	37905259	2023	Geriatric presentation of Boerhaave's syndrome	Chest X-ray, CT angiography	Thoracic drainage, antibiotics, esophageal prosthesis	Discharged after 48 days
J Am Coll Surg	Bakhos *et al* [18]	25053221	2014	Spontaneous pneumomediastinum analysis, discussing management strategies	Retrospective review	Conservative management	Excellent prognosis, low recurrence risk

CT: Computed tomography; VATS: Video-assisted thoracic surgery.

Clinical significance

The clinical significance of this study lies in its reminder to clinicians to maintain a high level of vigilance, particularly when managing patients presenting with nonspecific chest symptoms and lacking typical triggers. Although the clinical diagnosis of esophageal rupture has traditionally relied on typical triggers, such as severe vomiting or swallowing difficulties, this study demonstrates, through case presentation, that atypical triggers such as severe coughing can also lead to esophageal rupture. This finding broadens the understanding of the potential causes of esophageal rupture and suggests that clinicians should consider a wider range of possibilities to avoid missed or misdiagnosis. Therefore, this study emphasizes that the clinical diagnosis of esophageal rupture should not be confined to traditional diagnostic criteria but should also include heightened awareness of atypical symptoms.

Furthermore, this study highlights the importance of individualized treatment strategies, especially when dealing with spontaneous esophageal rupture, an acute and severe condition. The research indicates that early diagnosis and precise treatment can significantly improve patient outcomes, particularly in early cases without major complications, where conservative treatment can effectively control the condition. However, for patients with more severe presentations, prompt surgical intervention is essential. Therefore, this study provides clinical guidance on how to select treatment options based on the patient's specific condition and trigger, underscoring the critical role of rapid and accurate treatment decisions in improving survival rates and reducing complications.

Diagnostic challenges and treatment considerations

The diagnostic challenge of spontaneous esophageal rupture primarily arises from its nonspecific clinical manifestations, such as chest pain, difficulty breathing, and subcutaneous emphysema, which overlap with various chest diseases. Therefore, clinicians need to conduct a comprehensive evaluation combining patient history, physical examination, and imaging studies (such as chest X-ray and esophagography) to accurately rule in or out the diagnosis. Additionally, due to the rarity of this condition, it may not be considered in the initial differential diagnosis, leading to delayed diagnosis and increased patient risk. Treatment strategies should be individualized based on the patient's clinical condition, the size and location of the rupture, and any associated complications, in order to optimize treatment outcomes and improve prognosis.

Future research directions

This study not only provides important guidance for current clinical practice but also offers new perspectives and directions for future research. Firstly, future studies should further explore the impact of atypical triggers on the pathogenesis of esophageal rupture, such as coughing, excessive straining, and other factors, particularly in high-risk populations such as the elderly and patients with pulmonary diseases. These studies will help identify at-risk groups earlier in clinical settings, thereby improving early diagnosis rates of the disease.

Additionally, with ongoing advancements in technology, the application of artificial intelligence and imaging techniques holds great promise for the early diagnosis of esophageal rupture. By analyzing large volumes of imaging data, artificial intelligence can assist clinicians in making more accurate diagnoses in a shorter amount of time, especially when dealing with atypical cases. Future research should also explore how emerging technologies such as modern endoscopy, laparoscopy, and artificial intelligence can be integrated to achieve more precise diagnoses and personalized treatment plans. This integration could improve treatment outcomes and shorten recovery times for patients.

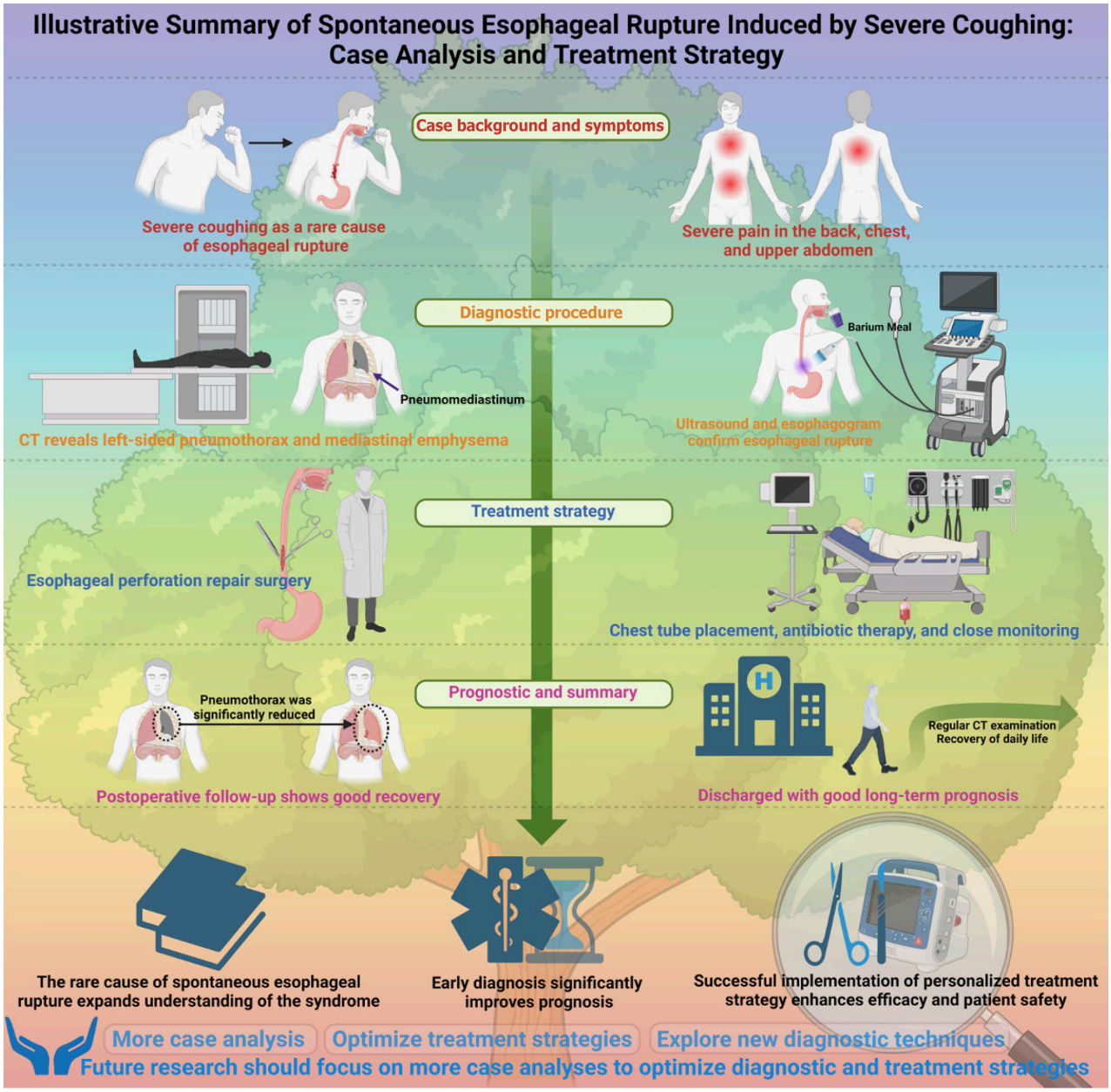


Figure 4 Illustrative summary of spontaneous esophageal rupture induced by severe coughing: Case analysis and treatment strategy. CT: Computed tomography.

In summary, the clinical findings of this study offer new insights into the early diagnosis and treatment of esophageal rupture, laying a foundation for future related research. Further investigations will not only deepen our understanding of this condition but also drive the development of more efficient and accurate treatment strategies, ultimately improving patients' quality of life and prognosis.

CONCLUSION

This study emphasizes the importance of early recognition of spontaneous esophageal rupture (Boerhaave syndrome), particularly when atypical symptoms are present. Clinicians must maintain a high level of vigilance, as this condition is often misdiagnosed or diagnosed late due to its nonspecific symptoms. Early identification not only helps prevent the progression of the disease but can also significantly improve patient prognosis (Figure 4). Furthermore, this study highlights the critical role of individualized treatment strategies. Given the variations in clinical presentations among different patients, standardized treatment protocols often fail to meet the needs of all patients. Therefore, developing personalized treatment plans is essential for improving efficacy and reducing complications. Clinicians should be prepared to adjust treatment approaches flexibly based on the patient's response, thereby enhancing overall treatment outcomes.

FOOTNOTES

Author contributions: Xiong SY and Liu CJ conceived and designed the study; Li YF, Zhang HL, and Chen XW performed the experiments; Wang HM analyzed the data; Chen JC wrote the manuscript; All authors reviewed and approved the final version of the manuscript.

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CASE REPORT

Gastric adenocarcinoma of fundic gland mucosa arising in heterotopic gastric mucosa of the duodenum: A case report

Qun-Ying Yang, Jing Xu, Jian-Wen Hu, Xiao-Dong Huang

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Abstract

BACKGROUND

Heterotopic gastric mucosa (HGM) is the most common type of epithelial heterotopia, which can occur in any part of the gastrointestinal tract. The duodenum is one of the common sites of HGM. HGM is usually considered benign, and malignant transformation of HGM in the duodenum is extremely rare.

CASE SUMMARY

We reported a middle-aged man admitted to the hospital due to abdominal pain, whose gastroduodenoscopy revealed a polypoid uplift in the duodenum. The attending physician directly removed the lesion using a snare, histopathological analysis demonstrated multidirectional cellular differentiation on the basis of duodenal HGM. The hematoxylin and eosin stains of the duodenal lesion demonstrated HGM, the superficial mucosa exhibited gastric foveolar-type epithelium, numerous mucous glands were identified beneath the foveolar region. Additionally, focal areas displayed several signet-ring cell changes. Gastric foveolar-type epithelium was diffusely positivity for MUC5AC and Ki67. Numerous mucous gland was positivity for MUC6, partially positive for MUC2, pepsinogen I and H^+/K^+ ATPase. It was eventually diagnosed gastric adenocarcinoma of fundic gland mucosa on the basis of duodenal HGM.

CONCLUSION

We reported the first case of gastric adenocarcinoma of fundic gland mucosa arising in the duodenum on the basis of HGM. Although HGM is mostly benign, there is also a risk of carcinogenesis.

Key Words: Gastric adenocarcinoma of fundic gland mucosa; Heterotopic gastric mucosa; Histopathological analysis; Oxyntic gland; Endoscopic mucosal dissection; Case report

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Core Tip: This case represents the first reported of gastric adenocarcinoma of fundic gland mucosa in the duodenum arising from heterotopic gastric mucosa. The article highlights a rare occurrence, which could be of great interest to medical professionals encountering similar cases. The collaboration between the gastroenterology and pathology departments in different hospitals shows the importance of interdisciplinary teamwork in diagnosing and treating complex medical cases.

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INTRODUCTION

Heterotopic gastric mucosa (HGM) has histological characteristics of gastric mucosa, but it is located outside the gastric border and may occur anywhere from the oral cavity to the rectum[1]. The esophagus is the most common site of HGM, followed by the duodenum. The incidence of HGM in the duodenum is reported to range from 0.51% to 8.9%[1-3]. HGM in the duodenum can present as polyps, lateral growth, submucosal lesions, and other growth patterns[4]. It is believed that HGM in the duodenum mainly presents as polypoid lesions[2,5]. Oftentimes, polypoid ectopic gastric mucosa found incidentally during endoscopy is asymptomatic in patients[6]. Primary duodenal cancer is one of the rarest cancers in the gastrointestinal tract, and malignant transformation caused by HGM is extremely rare[7]. Gastric fundic gland neoplasms represent a rare form of gastric neoplasia, distinguished by their differentiation towards the fundic glands. Based on infiltration and cellular differentiation characteristics, it can be classified into oxyntic gland adenoma, gastric adenocarcinoma of the fundic gland, and gastric adenocarcinoma of fundic gland mucosa (GA-FGM). Our case represents the first reported of GA-FGM in the duodenum arising from HGM.

CASE PRESENTATION

Chief complaints

A 55-year-old male was admitted to the hospital for intermittent abdominal pain lasting 5 years.

History of present illness

For the past 5 years, the patient had recurrent mild abdominal pain, with the main location being the upper abdomen and around the navel, without nausea or vomiting, without acid reflux or heartburn, without a feeling of food blockage, occasionally with small amount of bloody stools.

History of past illness

The patient had hypertension for 6 years and was undergoing medication treatment.

Personal and family history

The patient denied smoking and drinking habits, and all family members were in good health.

Physical examination

On examination, his body temperature was 36.7 °C, pulse rate 68 beats/minute, respiratory rate 18 breaths/minute, blood pressure 134/92 mmHg, and oxygen saturation 100% on room air.

Laboratory examinations

All blood test results, including tumor markers, were within normal limits. Routine stool examination and occult blood test showed no abnormalities. Enhanced computed tomography scan of the whole abdomen and colonoscopy showed no significant abnormalities.

Imaging examinations

Upper gastrointestinal endoscopy revealed chronic non-atrophic gastritis and a 0.8 cm × 1.2 cm polypoid uplift in the duodenal bulb (Figure 1A). The attending physician directly removed the lesion using a snare, and the wound was closed

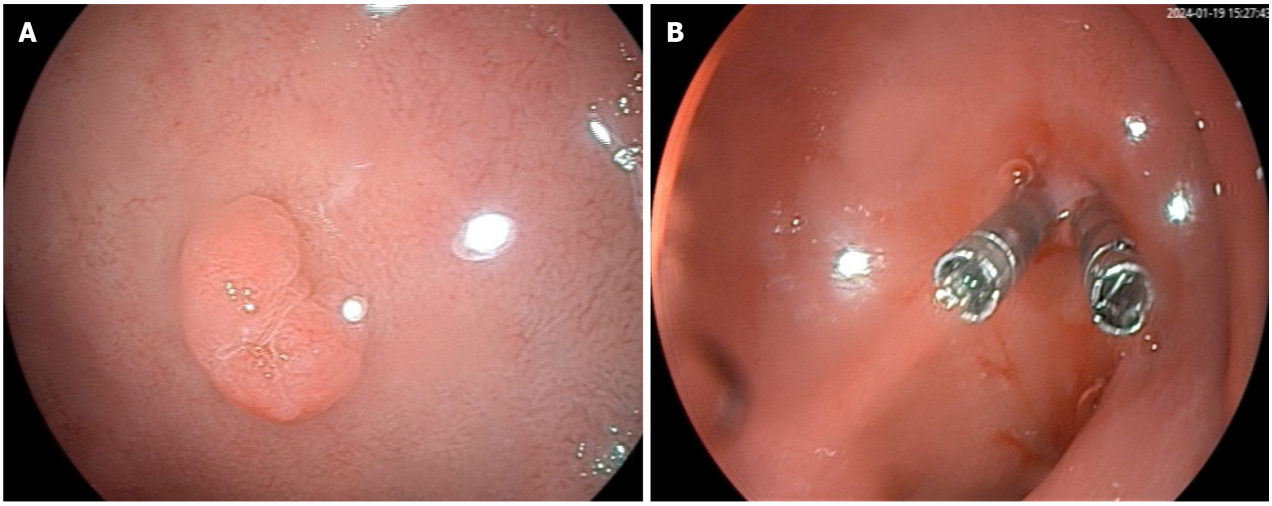


Figure 1 A polypoid uplift was identified in the duodenal bulb during gastroscopy in in a middle-aged male. A: Upper gastrointestinal endoscopy revealed a 0.8 cm × 1.2 cm polypoid uplift in the duodenal bulb; B: This lesion was removed by a snare and the wound was closed with two titanium clips.

with two titanium clips (Figure 1B).

In the presented case, hematoxylin and eosin staining and immunohistochemical analysis demonstrated obvious gastric fundus gland structure and multidirectional cellular differentiation, which were predominantly composed of three distinct components (Figure 2). Firstly, the superficial mucosa exhibited gastric foveolar epithelium, which was extensively positive for MUC5AC (Figure 2A and D), with certain regions demonstrating intraluminal papillary growth, branching, serration, and bicolored cytoplasm, notably lacking mucous caps. The nuclei appeared round and deeply stained. Coupled with the high proliferative activity indicated by Ki-67 (Figure 2E), these findings are entirely consistent with foveolar epithelium high-grade intraepithelial neoplasia. Secondly, except for focal residual normal oxyntic glands, numerous mucous glands were observed. Immunohistochemical staining of these mucous glands revealing MUC6 (Figure 2F), positivity, partial positivity for pepsinogen I (Figure 2H), and H^+/K^+ ATPase (Figure 2I), and scattered Ki67 positivity. These findings are consistent with a tumor exhibiting differentiation towards oxyntic glands. Thirdly, in the deepest region of the mucosa adjacent to the muscularis mucosae, scattered dilated glands were observed (Figure 2B), which exhibiting disrupted glandular polarity, occasional intraglandular papillary growth, and nuclei arranged in a double layer. The cytoplasm contained small vacuoles, reminiscent of immature goblet cells. Additionally, focal areas displayed several signet-ring cell changes (Figure 2C), dispersed throughout the tissue. Regrettably, the glands initially observed in the hematoxylin and eosin stains were no longer detectable following deeper sectioning for immunohistochemistry. Only a few transversely elongated glands remained, which were partially positive for MUC5AC, MUC6, and MUC2 (Figure 2G), and high proliferative Ki67 activity. Although direct evidence is lacking, we hypothesize that this region of the tumor has undergone enterotype differentiation and may also contain a poorly differentiated component.

MULTIDISCIPLINARY EXPERT CONSULTATION

These poorly differentiated small mucinous vacuoles in the glands need to be distinguished from the cytoplasmic vacuolization caused by proton pump inhibitors, according to some pathological experts. However, considering the poor prognosis of signet ring cell carcinoma, surgical resection is recommended for patients. The patient rejected surgery and underwent endoscopic mucosal dissection (ESD) 2 months later.

FINAL DIAGNOSIS

The patient was ultimately diagnosed with GA-FGM arising from HGM of the duodenum, which also had included intestinal-type and a few suspected low-differentiation components.

TREATMENT

The patient underwent ESD 2 months later. Duodenal mucosa was observed under the postoperative specimen microscope, part of the surface intestinal epithelium was replaced by gastric foveolar epithelium, with papillary growth, some retaining the mucous cap of gastric concave and some missing the mucous cap, and the nuclei were arranged in pen-shaped pseudolamellar arrangement. Therefore, these residuary glands were considered to be low-grade intraepithelial neoplasia. No signet-ring cell change were observed in the postoperative pathological sections.

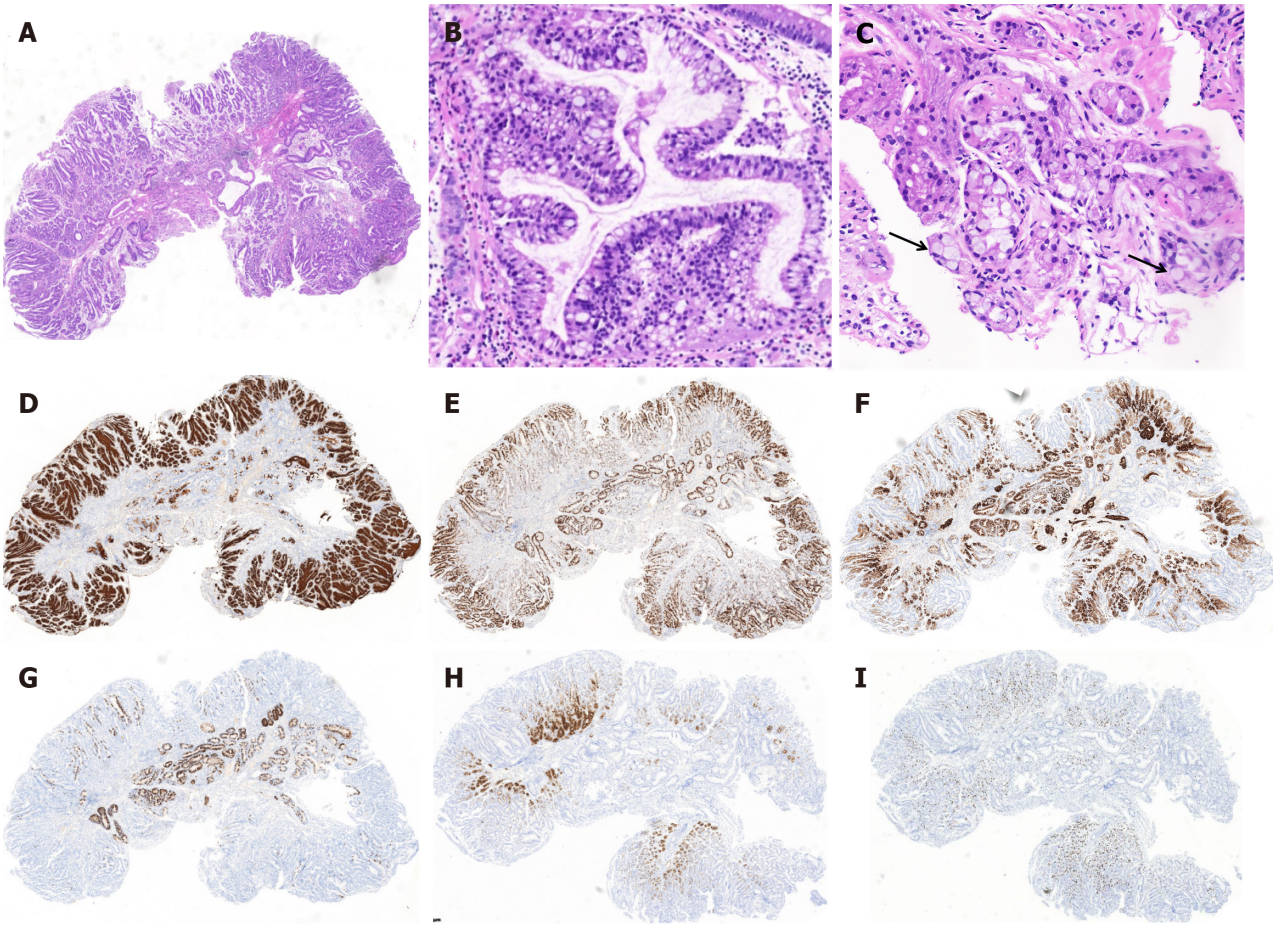


Figure 2 Representative hematoxylin and eosin staining and immunohistochemical analysis images from a case involving a middle-aged male patient diagnosed with gastric adenocarcinoma of the fundic gland mucosa. A: The superficial mucosa exhibited gastric foveolar-type epithelium, numerous mucous glands were observed immediately below the epithelium; B: Scattered dilated glands were observed in the deepest region of the mucosa; C: Focal areas displayed several signet-ring cell changes (black arrow); D-I: Gastric foveolar-type epithelium was diffusely positivity for MUC5AC (D) and Ki67 (E); mucous glands were positivity for MUC6 (F), partially positive for MUC2 (G), pepsinogen I (H) and H+/K+ ATPase (I).

OUTCOME AND FOLLOW-UP

A follow-up gastroscopy around 2 months post-ESD did not reveal any significant abnormalities. The follow-up is ongoing.

DISCUSSION

HGM is frequently identified in duodenal elevated lesions, especially in the duodenal bulb[2]. HGM is defined as the presence of gastric mucosa outside of the stomach, which is documented by histologic finding[8]. Histologically, it resembles gastric body mucosa, with gastric foveolas and oxyntic glands. The presence of oxyntic glands facilitates the secretion of gastric acid and pepsin, which may result in clinical symptoms. However, due to the neutralization of gastric acid and pepsin by duodenal fluid, clinical symptoms of HGM in the duodenum are often atypical, only occasionally discovered during gastroscopy[1,2]. But cases of duodenal HGM have been reported due to symptoms such as bleeding, narrowing, and even malignancy[9-11].

A report showed that among the 137 patients with duodenal ulcer, 76 cases (55%) had HGM in the obtained specimens, suggesting that HGM was strongly associated with concurrent duodenal ulcer[10]. In clinical practice, small polyps in the duodenum are mostly considered benign and rarely biopsied. Duodenal ulcers are rarely biopsied unless malignancy is suspected. Therefore, we believe that the incidence of HGM in the duodenum may be underestimated. Therefore, early biopsies for HGM in the duodenum should be performed for accurate diagnosis and further management to prevent the risk of malignant transformation.

HGM is essentially a benign entity, with the occurrence of malignant transformation being exceedingly rare. However, it is a potential precursor to pyloric gland adenoma and gastric phenotype adenocarcinoma[12]. A Japanese report showed that 3.4% of early carcinomas of the duodenal bulb arise from HGM[13]. The mechanism of carcinomatosis is considered the metaplasia-dysplasia-carcinoma sequence or adenoma-carcinoma sequence, as in other epithelial tissues. *Helicobacter pylori* infection is the greatest risk factor for gastric cancer (GC)[14].

But GA-FGM may be a subtype of *Helicobacter pylori*-negative GC[15]. Some studies proposed naming tumors showing differentiation toward fundic glands and foveolar epithelium-like differentiation as GA-FGM[16,17]. Although GA-FGM is no longer a rare case in the stomach, there have been no documented cases involving the duodenum. This case represents the first reported of GA-FGM in the duodenum arising from HGM. The preferred treatment modality comprises endoscopic interventions, such as endoscopic mucosal resection and ESD, as well as surgical resection.

The distinctiveness of this case is attributable not only to the presence of gastric fundic gland-type adenocarcinoma but also to the tendency of its transformation into enterotype. This phenomenon may elucidate why fundic gland-type tumors are typically identified in early-stage GC, with no documented occurrences in advanced stages. This phenomenon is likely attributable to the highly benign nature of fundic gland differentiation. However, as the tumor progresses and undergoes transformation into an intestinal or common type, it acquires the capacity for rapid advancement, thereby supplanting the most benign component.

CONCLUSION

In short, our case represents the first reported of GA-FGM in the duodenum arising from HGM. The growth pattern of ectopic gastric mucosa in the duodenum is diverse, with polyps being a common presentation. Therefore, the possibility of HGM should be considered in duodenal polypoid lesions. Although most HGMs are asymptomatic and benign, there is a possibility of malignant transformation. Early biopsy and appropriate treatment are crucial for reducing the risks of complications and malignant transformation.

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FOOTNOTES

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CASE REPORT

Adenocarcinoma originating from a colonic duplication cyst: A case report

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Abstract

BACKGROUND

Gastrointestinal duplication is a rare congenital anomaly of the digestive tract, with colonic manifestations being particularly uncommon. Malignant transformation of colonic duplication cysts is rare, with adenocarcinoma being the most frequently reported type. Herein, we report a rare case of adenocarcinoma originating from a colonic duplication cyst.

CASE SUMMARY

A 49-year-old woman was found to have an elevated cancer antigen 19-9 level during a routine checkup. Imaging revealed a well-defined abdominal cavity cystic mass, which was initially suspected to be an ovarian teratoma. Laparoscopic surgery revealed a duplication cyst, and pathological examination confirmed adenocarcinoma arising from the cyst. The mass within the transverse mesocolon was successfully excised by a colorectal surgeon. Immunohistochemical analysis confirmed adenocarcinoma with invasion into the muscularis propria. Postoperative endoscopy and positron emission computed tomography scan showed no signs of malignancy, except for an elevated cancer antigen 19-9 level. A multidisciplinary team recommended no further chemotherapy, advising routine follow-up for monitoring.

CONCLUSION

Colonic duplications, though rare, remain a differential diagnosis of unexplained abdominal masses, with complete resection being their primary treatment approach.

Key Words: Gastrointestinal duplication; Colonic duplication; Surgical resection; Adenocarcinoma; Malignant transformation; Case report

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Core Tip: In cases of gastrointestinal duplication involving cystic masses, maintaining a high suspicion for potential malignancy is crucial, even in asymptomatic patients. Due to the rarity of these conditions, a multidisciplinary approach is essential for accurate diagnosis and treatment. Comprehensive imaging studies, like contrast computed tomography, should evaluate the cyst's characteristics and its relation to adjacent structures. Surgical intervention, preferably through *en bloc* resection, is recommended to ensure complete removal of any neoplastic tissue. Regular follow-up and monitoring of tumor markers are vital for early detection of recurrence or progression.

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INTRODUCTION

Gastrointestinal duplication is an uncommon congenital anomaly, with gastrointestinal cystic or tubular abnormalities observed in any part of the gastrointestinal tract. The prevalence of congenital disease ranges from 1 in 4500 to 1 in 10000, with 80% of the cases diagnosed either before birth or within the first two years of life[1-4]. However, this condition may remain undetected until later in life.

The occurrence of gastrointestinal duplication has been reported in the ileum, ileocecal valve, and jejunum at rates of 30%, 30%, and 8%, respectively. However, its occurrence is rare in the colon and rectum, with incidences of 6%-7% and 5%, respectively[4-6]. If no related abnormalities are present, symptoms may not be observed until complications occur[5, 7]. Clinical symptom development depends on factors such as location, size, abnormal mucosa presence within the duplication site, adjacent bowel connection, and inflammation.

The main symptoms are abdominal pain and intestinal obstruction, while the other symptoms include the presence of an abdominal mass, chronic pain, constipation, and, less frequently, acute abdominal symptoms, including intestinal volvulus[8], intussusception, perforation, or active bleeding[9].

Herein, we present a case of adenocarcinoma arising from an asymptomatic duplication cyst in the colon of a 49-year-old female patient.

CASE PRESENTATION

Chief complaints

Detection of abnormal cancer markers.

History of present illness

A 49-year-old woman with no previous medical history presented to the gynecology outpatient clinic of a tertiary hospital with abnormal cancer markers detected during an examination at a local clinic.

History of past illness

There was no specific medical history such as diabetes, hypertension, or surgery.

Personal and family history

There was no specific personal and family history.

Physical examination

There were no abnormal findings in the physical examination upon admission.

Laboratory examinations

Elevated levels of cancer antigen (CA)-19-9: 61.6 U/mL, normal range: < 37 U/mL; CA-125: 47.3 U/mL, normal range: < 55 U/mL and normal levels of carcinoembryonic antigen: 1.1 U/mL, normal range: < 5 U/mL.

Imaging examinations

Abdominal-pelvic computed tomography (CT) revealed a well-defined 6.5 cm × 7.8 cm × 8.5 cm cystic mass with internal fatty attenuation and fluid-fluid level in the right adnexa without enhancement (Figure 1). The gynecology department at our hospital uses diagnostic laparoscopy to differentiate extragonadal teratomas, ovarian teratomas, and myxoid

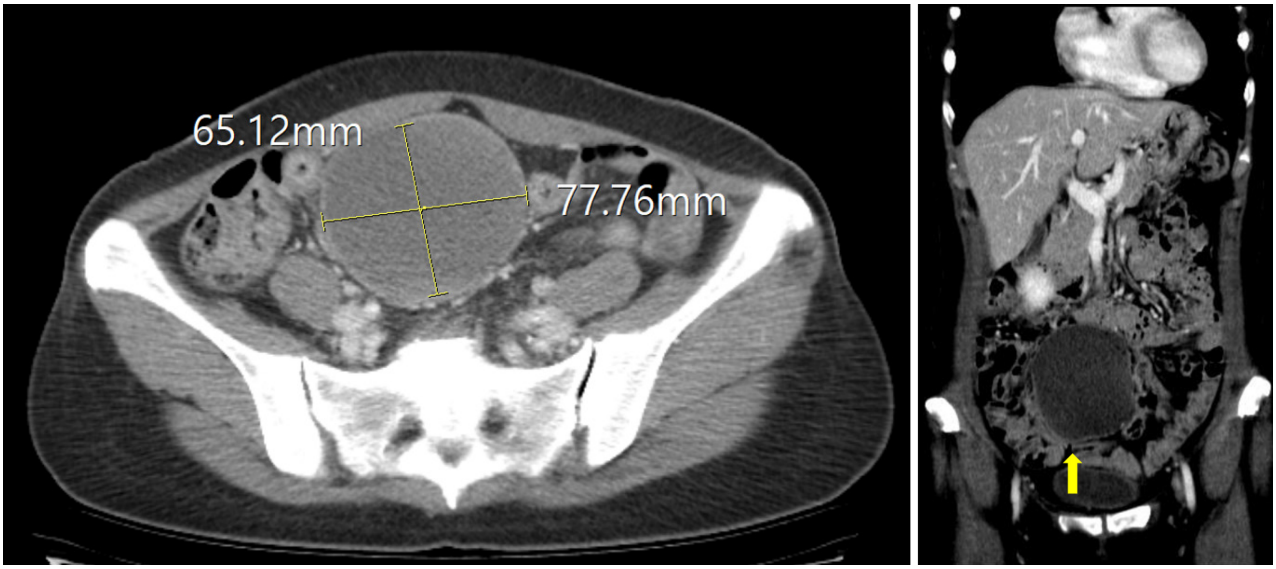


Figure 1 Preoperative radiologic findings. A 6.5 cm × 7.8 cm × 8.5 cm well-defined cystic mass with internal fatty attenuation and a fluid-fluid level was identified in the right adnexa, without enhancement. The differential diagnoses includes extragonadal teratoma, ovarian teratoma, and, less likely, myxoid liposarcoma. The absence of clear continuity with the ovary suggests an extragonadal teratoma, although an ovarian teratoma cannot be excluded if continuity is obscured by the scan slice thickness.

liposarcomas. During laparoscopy, the cyst had no communication with the ovaries; however, it was in the transverse mesocolon (Figure 2A).

MULTIDISCIPLINARY EXPERT CONSULTATION

As this case was rare, we discussed the treatment plan for the patient at a multidisciplinary treatment, consisting of a colorectal surgeon, oncologist, pathologist, radiologist, and gastroenterologist, conference and concluded that no further chemotherapy was needed due to the complete surgical resection. Regular checkups were recommended.

FINAL DIAGNOSIS

The cyst was diagnosed as adenocarcinoma originating from a colonic duplication cyst with muscularis propria invasion (Figure 3).

TREATMENT

As the tumor was hard and did not adhere to the floor and was capable of movement, a mini-laparotomy procedure was performed (Figure 2B). The cyst was then separated from the colon, mobilized, and excised by a colorectal surgeon. The well-defined cystic mass did not communicate with the colon, and no damage to the colon was observed after the resection. The patient was discharged without any postoperative complications.

Immunohistochemical analysis revealed that the tumor cells were positive for cytokeratin (CK) 7, CK 20, and caudal-type homeobox transcription factor 2 (Table 1).

OUTCOME AND FOLLOW-UP

Postoperatively, endoscopy revealed no abnormal lesions. Moreover, whole-body positron emission tomography revealed no abnormal hypermetabolic lesions suggesting malignancy (Figure 4). CA 19-9 levels measured 1 month post-surgery were 9.3 U/mL, which was within the normal range (< 37 U/mL); no other specific findings were observed. No evidence of recurrence has been observed two years post-surgery.

Table 1 Pathology results

Variables	Results
Preoperative treatment	Not done
Gross type	Other (cystic)
Tumor location	Transverse colon, mesentery
Histologic variant (World Health Organization 5th ed.)	Not otherwise specified
Histology grade	Moderately differentiated
Tumor size	9.2 cm × 8.0 cm × 7.8 cm
Invasion margins	Muscularis propria
Resection margins	Safety margin: Radial 02 cm
Lymph node	Not submitted
Lymphatic invasion	Not identified
Venous invasion	Not identified
Perineural invasion	Not identified
Tumor deposits	Not identified
Tumor budding	Negative (× 1/200)
Tumor border	Infiltrative
Stromal reaction	Absent
Preexisting adenoma	Not identified
Associated findings	None
Caudal-type homeobox transcription factor 2	Positive
Cytokeratin 20	Positive
Cytokeratin	Positive
Estrogen receptor	Negative
Paired box gene 8	Negative

DISCUSSION

Gastrointestinal duplications are uncommon congenital abnormalities diagnosed during the prenatal period or within the first two years of life in approximately 80% of cases[2,3]. Colonic duplications account for only 13% of all duplications and arise in the cecum[3,10]. Although malignant transformation in a duplication is rare, cases of adenocarcinoma, squamous cell carcinoma, carcinoid tumors, gastrointestinal stromal tumors, and leiomyosarcoma have been reported. In these rare cases, adenocarcinoma is the predominant histological malignancy type[11-14]. The duplication diagnosis is based on well-established morphological criteria, including: (1) Direct attachment to the alimentary tract; (2) Presence of a smooth muscle layer; and (3) A lining epithelium similar to that of the alimentary tract[11]. Our case met criteria 2 and 3, leading to a diagnosis of adenocarcinoma arising from a colonic duplication cyst.

The diagnosis of colonic duplications may be challenging. In children before the age of 2 years, it is often diagnosed by intrauterine ultrasonography; however, in adults, it is often revealed during surgery[3,15-17]. Contrast CT is the most effective method for establishing a diagnosis and determining the cyst composition and its interaction with adjacent structures[18]. The cysts usually have attenuation levels comparable to that of water with a discernible calcification rim in some cases[11]. The differential diagnoses include colonic duplication cyst, primary colonic malignancy, atypical gastrointestinal stromal tumor, intestinal lymphoma, myxoid liposarcoma, or loculated perforation. In women, ovarian teratoma and extragonadal teratoma should also be considered. However, a definitive diagnosis is often challenging to establish preoperatively, and surgical resection is frequently required to confirm the final pathological diagnosis[19]. In this case, a well-defined cystic mass with internal fatty attenuation and fluid-fluid level was observed; however, ovarian teratoma was more likely than colon duplication. Furthermore, nuclear medicine scans can reveal duplications in the stomach mucosa, whereas contrast enema or colonoscopy may be useful in cases in which there is a link to the colonic lumen.

Previous studies have reported colonic duplication causing intussusception, rectal hemorrhage, and pancreatitis, with abdominal pain and a palpable mass being the most common symptoms in adenocarcinoma cases[11]. In this case, the condition was detected during a regular checkup without specific symptoms.

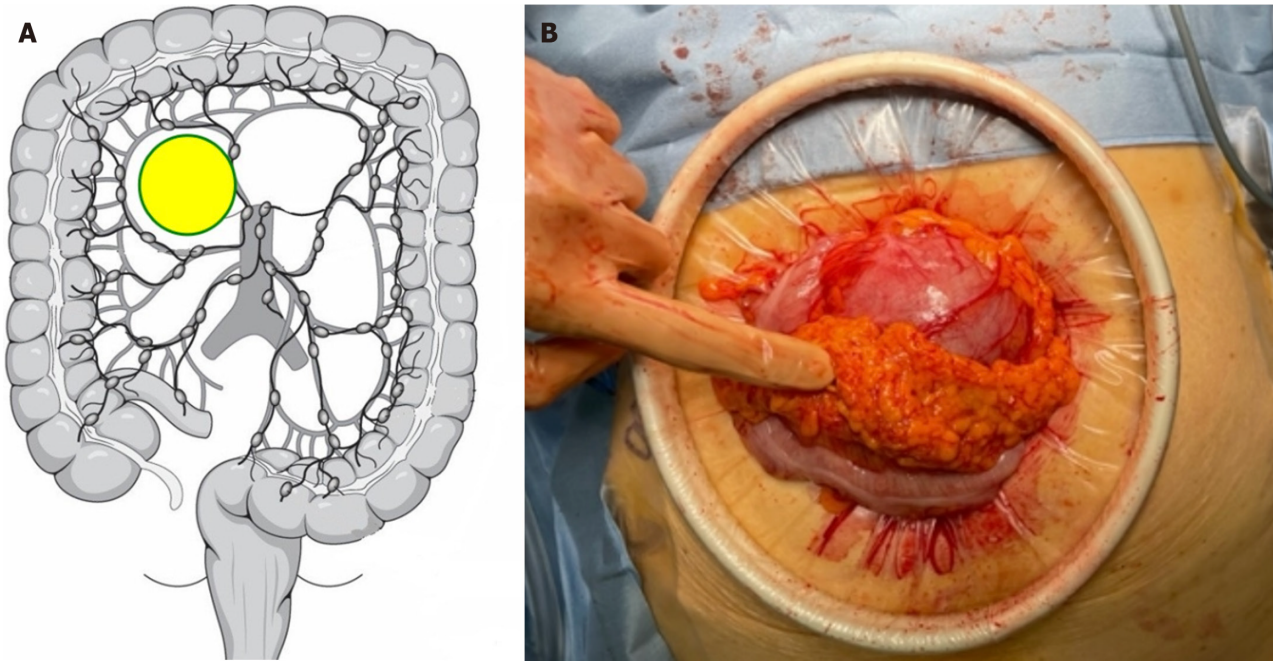


Figure 2 Colonic duplication location. A: Intraoperative findings of colonic duplication; B: Following mini-laparotomy, colonic duplication was observed adjacent to the colon and attached to the omentum.

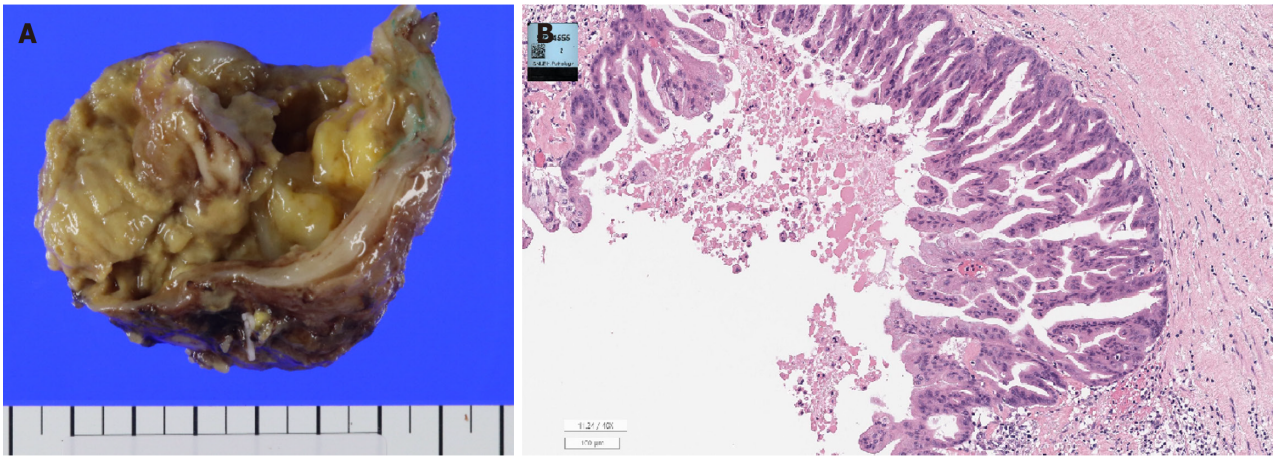


Figure 3 Gross pathologic finding. A: A cystic tumor section encased in a serosal layer revealed an internal cavity filled with mucinous-like material. Histological and pathological findings; B: The cyst wall was lined with epithelium resembling the intestinal mucosa, with mucin occupying the lumen, and mild inflammatory cell infiltration was observed in the surrounding stroma.

Colonic duplication is primarily managed through *en bloc* resection of the adjacent large intestine[2,10]. In selected cases without damage to the bowel wall or vascular supply, enucleation of duplication cysts may be performed alternatively[2]. Furthermore, advances in laparoscopic procedures and instrumentation have enabled laparoscopic resection [10]. In this case, a gynecologist attempted to approach the tumor laparoscopically and confirmed that it was distant from the uterus and ovaries and adjacent to the transverse colon. A colorectal surgeon then completed the duplication cyst resection, separating the colon and duplication cyst *via* mini-laparotomy, without damaging the colonic wall or blood vessels. Lymph node dissection was not performed because no malignancy was suspected.

The potential for colonic duplication cysts and malignancy warrants consideration of the extent of resection *via* a multidisciplinary approach; however, this team was not assembled before surgery. Following the postoperative adenocarcinoma confirmation, a multidisciplinary group was organized to assess the pathological findings and postoperative evaluations. Although lymph node dissection was not performed, further assessment revealed no increase in lymph node uptake or enlargement, and no high-risk characteristics were revealed by pathology. Therefore, complete surgical resection was considered appropriate, adjuvant chemotherapy was not administered, and routine surveillance was performed.

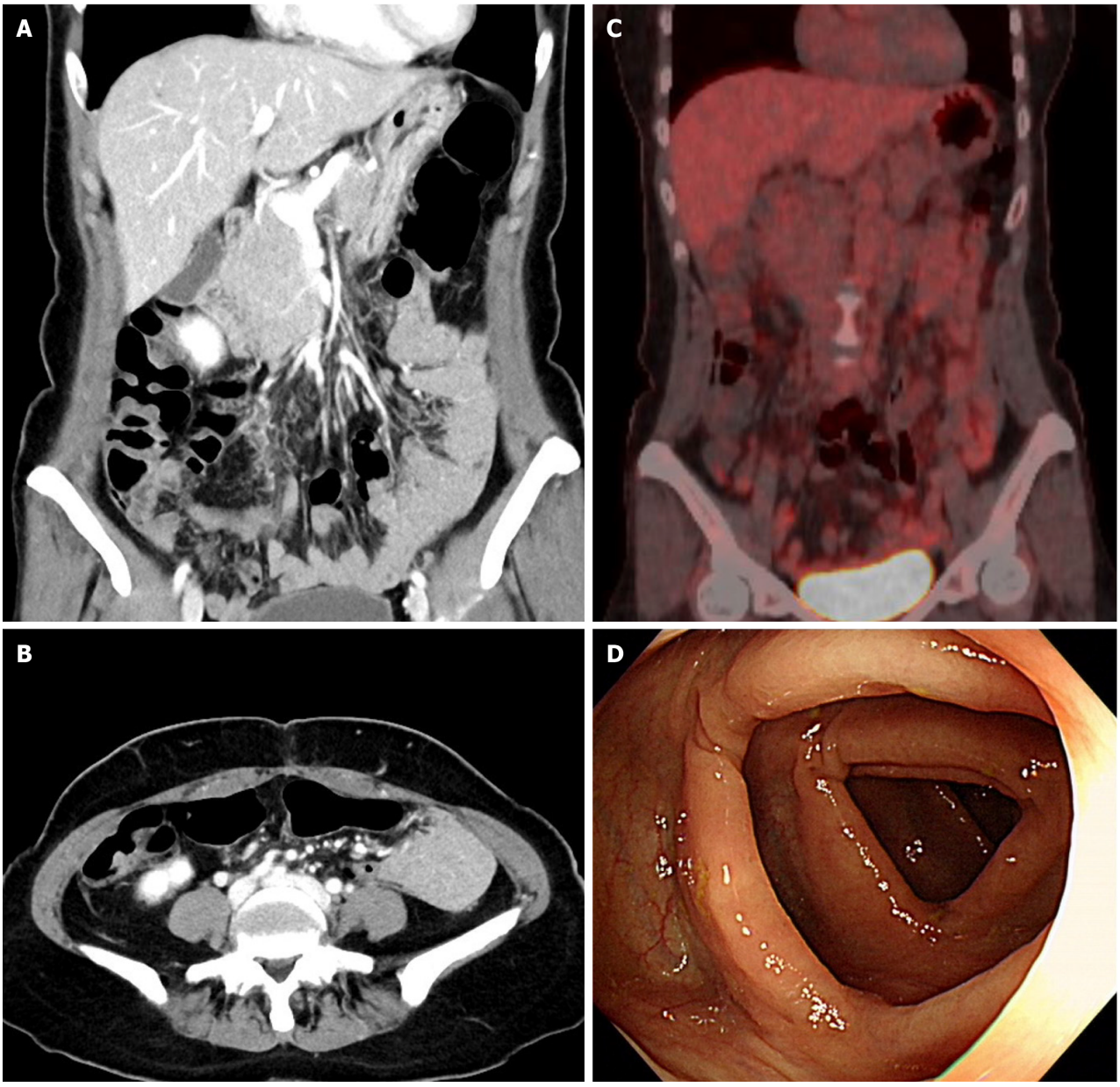


Figure 4 Postoperative imaging and endoscopy findings. A and B: Postoperative abdominal-pelvic computed tomography scans show no detectable intra-abdominal masses; C: Postoperative positron emission computed tomography-computed tomography reveals no abnormal hypermetabolic lesions suggestive of malignancy; D: Postoperative colonoscopy demonstrates no abnormal lesions in the colon.

CONCLUSION

Colonic duplication is an uncommon congenital anomaly, and malignant transformation is extremely rare. When assessing a cystic mass adjacent to or enclosed by the gastrointestinal tract, duplication should be considered in the differential diagnosis. The potential for malignancy arising from a duplication cyst should be considered, and thorough *en bloc* resection of the tumor is imperative.

FOOTNOTES

Author contributions: Lee J contributed to data curation and drafting of the manuscript; Suh JW conducted the review and editing of the manuscript.

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CASE REPORT

Type III choledochal cyst confirmed by aspiration and treated with endoscopic fenestration plus internal drainage: A case report

Zi-Meng Wang, Song Su, En-Qiang Ling-Hu, Ning-Li Chai

Specialty type: Gastroenterology and hepatology

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Abstract

BACKGROUND

Type III choledochal cysts (CCs) are extremely rare, and they present as dilatations and herniations of the end of the common bile duct into the duodenum. Moreover, type II CCs may be easily misdiagnosed as intraduodenal polyps or tumors. Thus, adequate differential diagnosis and selection of appropriate treatment are important.

CASE SUMMARY

A young man with a duodenal mass presented with 3-year intermittent abdominal pain and acute pancreatitis 3 days before hospitalization. After evaluation by magnetic resonance imaging and endoscopic ultrasonography, the duodenal papilla was pressed, and the bile flowed out slowly, which was speculated to be the cause of his symptoms. The lesion was punctured with a submucosal injection needle, and golden clear fluid was aspirated. Laboratory tests of the aspirate after 50-fold dilution revealed significantly elevated total bilirubin, direct bilirubin, amylase and lipase. Taken together, these findings confirmed that the lesion was a type III CC. The patient underwent fused surgical procedures. Fenestration plus internal drainage of the lesion was subsequently performed with a DualKnife. After drainage, the incision was sealed with tissue clips. During follow-up, the patient recovered well, and no abdominal pain symptoms or acute pancreatitis recurred.

CONCLUSION

Laboratory tests of cyst aspirates are beneficial for diagnosis, and endoscopic fenestration plus internal drainage works well to mitigate cysts.

Key Words: Choledochal cyst; Aspiration; Drainage; Endoscopic ultrasound; Magnetic resonance imaging; Case report

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Core Tip: In adults with duodenal masses, the possibility of choledochal cysts should be considered. Endoscopic puncture and laboratory examination of aspirates can effectively assist in clarifying the diagnosis. For patients who refuse surgical treatment, endoscopic fenestration plus drainage is a safe, minimally invasive option that provides effective symptomatic relief. Furthermore, long-term periodic follow-up and monitoring utilizing serological tests and imaging are essential.

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INTRODUCTION

Choledochal cysts (CCs) are congenital cystic dilatations of the biliary tree[1]. Most CCs are diagnosed in childhood, with only 25% of CCs identified in adults. The incidence of CCs is 1:100000-150000 in Western populations, and the incidence of CCs is higher in Asian populations, with an incidence of 1:1000[2,3]. The exact cause of CCs remains unknown. Todani classification is the most widely used classification for CCs[4]. Type I CCs are the most common type, followed by type IV CCs[5]. Type III CCs are rare in both the children and adult population but occur more frequently in adults[6]. Surgical resection is the mainstay of treatment for CCs. The present case report emphasizes the comprehensive differential diagnosis of CCs by combining laboratory tests and imaging, and it introduces an option for treatment when the patient refuses surgery.

CASE PRESENTATION

Chief complaints

A 19-year-old Chinese man was referred to gastroenterology at our center with the complaint of intermittent abdominal pain for 3 years, with aggravated pain for 3 days prior to hospitalization.

History of present illness

The patient had intermittent abdominal pain with no apparent cause 3 years prior, which occurred every 1-2 months. The cause of the abdominal pain was unclear because there was no further diagnosis or treatment. The patient's abdominal pain worsened 3 days prior, mimicking colic symptoms. Laboratory tests revealed a lipase level of 2551.6 U/L (reference range: 13-60 U/L) and an amylase level of 720.1 U/L (reference range: 0-150 U/L). Abdominal computed tomography (CT) revealed pancreatic swelling, suggesting the possibility of pancreatitis. Abdominal ultrasound and CT did not reveal obvious biliary tract structural abnormalities or bile duct stones. The patient was initially diagnosed with acute pancreatitis (AP) at the local hospital, and his symptoms were relieved after early treatment with ulinastatin, octreotide acetate, and omeprazole. The patient was referred to our department for further etiologic diagnosis.

History of past illness

The patient's blood lipids were normal in previous examinations. The patient denied any other history of disease.

Personal and family history

The patient had no history of alcohol consumption. No significant family history was reported.

Physical examination

Physical examination revealed abdominal tenderness without rebound tenderness, and no abdominal masses were detected.

Laboratory examinations

Laboratory tests revealed a lipase level of 232.5 U/L (reference range: 13-60 U/L) and an amylase level of 196.5 U/L (reference range: 0-150 U/L). Liver and kidney function tests and tumor marker analysis revealed normal results. Analysis of immunoglobulin G (IgG) levels showed an IgG4 level of 248.0 mg/dL (reference range: 3-201 mg/dL) and an IgG1 level of 1030.0 mg/dL (reference range: 405-1011 mg/dL). Because the IgG4 and IgG1 levels were not significantly elevated, there was little likelihood of autoimmune pancreatitis.

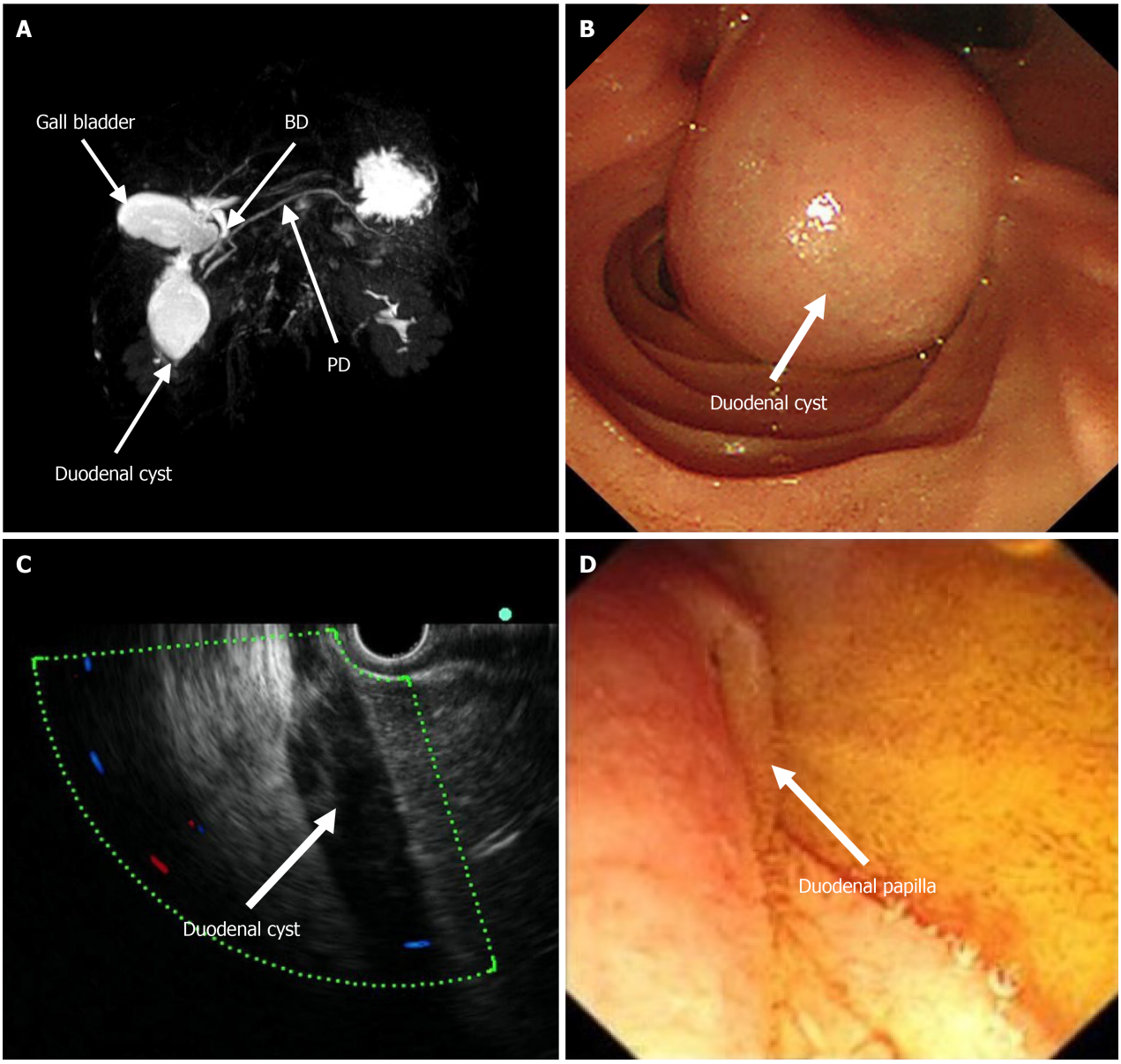


Figure 1 Imaging of the patient prior to treatment. A: Magnetic resonance imaging revealed a duodenal cyst with normal bile and pancreatic ducts; B: Endoscopy revealed a cystic mass in the descending part of the duodenum; C: Endoscopic ultrasonography revealed a homogeneous hypoecho without blood flow; D: The duodenal papilla was pressed, and the bile flowed out under endoscopy. BD: Bile duct; PD: Pancreatic ducts.

Imaging examinations

Magnetic resonance imaging (MRI) revealed a duodenal cyst, and no abnormal stenosis or dilatation of the bile duct or pancreatic duct was observed (Figure 1A). Endoscopy revealed a cystic mass in the descending part of the duodenum with a smooth surface and a short diameter of approximately 3 cm (Figure 1B). The lesion had a soft texture. Endoscopic ultrasonography (EUS) revealed a homogeneous hypoecho without blood flow inside the lesion (Figure 1C). After careful evaluation, the duodenal papilla was pressed, and the bile flowed out slowly (Figure 1D), which was speculated to be the cause for his symptoms and AP onset. Subsequently, the lesion was punctured with a submucosal injection needle, and golden clear fluid was aspirated (Figure 2A). Dilute the aspirate 50-fold using a sample diluent of 0.9% sodium chloride. Laboratory tests of the 50-fold diluted aspirate revealed a total bilirubin level of 329.4 μmol/L (reference 0-21 μmol/L), a direct bilirubin level of 243.3 μmol/L (reference 0-21 μmol/L), an amylase level > 59605 U/L (reference 0-150 U/L), and a lipase level > 15000 U/L (reference 13-60 U/L), representing significantly elevated levels. Taken together, these findings confirmed that the lesion was a type III CC.

FINAL DIAGNOSIS

The lesion was diagnosed as a type III CC.

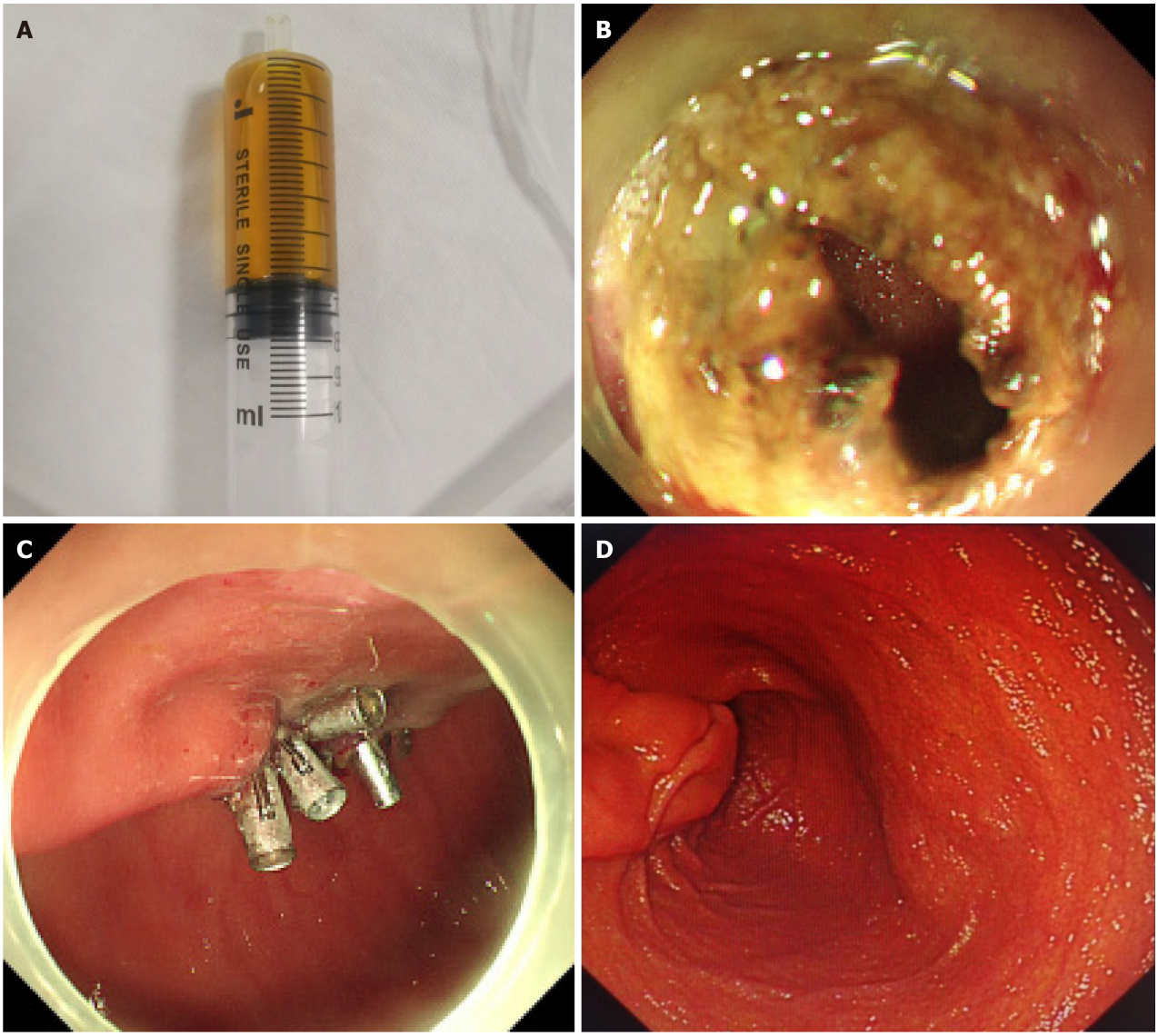


Figure 2 Images during patient treatment and follow-up. A: Clear yellow liquid was aspirated from the cyst; B: Fenestration of the mucosa; C: Closure of the incision with tissue clips; D: Gastroduodenoscopy showed good recovery without recurrence three months after treatment.

TREATMENT

The patient was fully informed of the treatment and risks involved with the surgery. Given the high risk and trauma of the surgery, the patient refused to undergo surgical treatment. Therefore, fenestration plus internal drainage of the lesion was performed using a DualKnife (Figure 2B). Yellow clear fluid was withdrawn after fenestration, and the inner surface of the cystic cavity was smooth. The lesion was subsequently squeezed repeatedly, and the lesion collapsed after the cystic fluid was extruded. After drainage, the incision was sealed with tissue clips (Figure 2C).

OUTCOME AND FOLLOW-UP

Post-treatment review showed a lipase level of 25.7 U/L (reference range: 13-60 U/L) and an amylase level of 74.9 U/L (reference range: 0-150 U/L). During follow-up, the patient recovered well, and no abdominal pain symptoms or AP recurred. Gastroduodenoscopy revealed no recurrence at three months after treatment (Figure 2D).

DISCUSSION

CCs are mostly congenital and more common in children. Approximately two-thirds of CCs present at age 10, but this disease can occur at all ages[7]. Although jaundice is common in early childhood, abdominal pain is a major symptom in adolescents and adults[8], as shown in the present case. Notably, such nonspecific symptoms, to some extent, lead to

delayed diagnosis. In the present case, the patient presented with intermittent nonspecific abdominal pain for 3 years without other gastrointestinal symptoms, during which the patient was not well examined nor definitively diagnosed. The patient was definitively diagnosed and etiologically treated only when the disease induced AP.

Abdominal ultrasound and CT can be used as preliminary tests to screen for abnormal biliary structures and bile duct stones[9]. However, these tests fail to identify the presence of anomalous pancreaticobiliary junctions[10]. MRI can show the location and morphology of the cyst well. EUS provides a safe and reliable examination method to explore the condition of the bile ducts and to make a differential diagnosis of the cystic nature. Notably, magnetic resonance cholangiopancreatography examination was not prioritized in the present case because the initial abdominal ultrasound and CT missed the identification of CCs. Laboratory tests were performed on aspirates from the cysts, which showed markedly elevated pancreatic enzymes and bilirubin, further clarifying the diagnosis. The supplemental laboratory tests offered new ideas for clinical diagnosis.

Treatment depends on the type of CC. Therapy for types I and IV CCs requires complete resection of the choledochus and restoration of bile flow, whereas the strategy for type II CCs includes simple cystectomy or diverticulectomy. Type III CCs can be treated with sphincterotomy or complete resection[11]. When a patient refuses surgical intervention, endoscopic fenestration plus internal drainage is an alternative and cost-effective option, providing a simple, less invasive and reproducible treatment. CCs are usually diagnosed and treated *via* surgery. However, the present patient was diagnosed with a CC *via* endoscopic aspiration. CC is often associated with pancreaticobiliary malunion, forming a common channel that typically has cystic fluid. To the best of our knowledge, the present case report is the first to provide laboratory results on the aspirate of a type III CC. Despite the low risk of transformation of type III cysts into malignant tumors, long-term follow-up with biochemical evaluation and abdominal ultrasound is suggested for optimal prognosis.

CONCLUSION

In summary, the possibility of a CC should be considered for duodenal masses, even in adults. MRI and EUS are helpful for diagnosis, while endoscopic aspiration and laboratory tests can confirm the diagnosis. Although surgical resection is the main treatment for CCs, endoscopic fenestration plus drainage could be an alternative treatment option for patients who refuse surgery.

FOOTNOTES

Author contributions: Wang ZM and Su S were directly involved in patient care, collected the data and drafted the manuscript; Chai NL performed the endoscopic diagnosis and treatment procedures; Ling-Hu EQ supervised the treatment and critically revised the manuscript.

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CASE REPORT

Laparoscopic management of intraductal oncocytic papillary neoplasm of the pancreas: Two case reports and review of literature

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Abstract

BACKGROUND

Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is an extremely rare pancreatic tumor, with only sporadic cases reported in the literature. IOPN is difficult to diagnose and highly prone to misdiagnosis. IOPN carries a certain risk of progressing to invasive cancer. Surgical resection is the primary treatment for IOPN. According to the existing literature reports, the vast majority of patients with IOPN of the pancreas undergo open surgery, while only one case of laparoscopic surgery have been reported.

CASE SUMMARY

This report presents two cases of IOPN in elderly female patients, aged 60 and 61. Both patients were asymptomatic, and their pancreatic masses were discovered incidentally. Preoperative diagnosis of IOPN is challenging and prone to misdiagnosis. In the first case, the patient underwent a laparoscopic distal pancreatectomy and splenectomy. The surgical procedure spanned 342 minutes, with an estimated intraoperative blood loss of around 100 mL. The patient experienced an uneventful postoperative recovery and was discharged on the 8th postoperative day. For the second case, a laparoscopic pancreaticoduodenectomy was performed. The operation lasted for 431 minutes with an intraoperative blood loss of approximately 50 mL. The patient also demonstrated a favorable postoperative course and was discharged on the 24th postoperative day. Postoperative pathology

and immunohistochemistry confirmed the diagnosis of IOPN. No recurrence was observed in either patient after follow-up periods of 8 and 10 months, respectively.

CONCLUSION
These cases demonstrate that laparoscopic surgery can be considered as one of the treatment options for IOPN of the pancreas.

Key Words: Intraductal oncocytic papillary neoplasm; Pancreas; Laparoscopic surgery; Misdiagnosis; Case report

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Core Tip: Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is extremely rare. The mechanism of the disease is not fully understood. Here, we reported 2 cases of pancreatic IOPN that were treated with laparoscopic surgery, covering its clinical manifestations, imaging findings, pathological morphological and immunophenotype, clinical treatment and prognosis, aiming to provide references for clinicians and improve the level of diagnosis and treatment of similar cases. Since a certain proportion of cases may be associated with invasive cancer, surgery is the preferred treatment. Laparoscopic surgery can be considered as one of the treatment options for IOPN of the pancreas.

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INTRODUCTION

Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is a rare pancreatic tumor and a precancerous lesion that may develop into pancreatic cancer. Pancreatic IOPN was first reported by Adsay *et al*[1] in 1996. Previously, pancreatic IOPN was believed to be a subtype of pancreatic intraductal papillary mucinous neoplasm (IPMN). However, due to its unique morphology, mucin content, and molecular characteristics, IOPN is now considered a high-grade intraepithelial neoplasm. Thus, in the new 2019 World Health Organization classification of digestive system tumors, IOPN is classified separately from IPMN[2,3]. Following the recent molecular and clinicopathological data revealing the rather substantial differences between IOPNs and IPMNs[4]. Specifically, IOPN does not exhibit the typical mutations observed in IPMN, such as *KRAS*, *GNAS*, and *RNF43*[5]. More recently, recurrent gene fusions have been described in genes encoding protein kinase A (*PRKACA* and *PRKACB*) in these tumors, which are not found in any of their clinicopathological differential diagnoses, further cementing their distinction as a separate entity. Furthermore, the clinical behavior is also distinct, demonstrating a significantly better prognosis than in IPMN, even in the context of metastasis and recurrence[6,7].

Currently, few articles have reported IOPN of the pancreas, and its pathogenesis and clinical features remain largely unclear. In addition, due to the lack of distinctive laboratory and imaging manifestations, preoperative diagnosis is challenging, and misdiagnosis is common. IOPN carries a certain risk of progressing to invasive cancer. Surgical resection is the primary treatment for pancreatic IOPN patients. According to the existing literature reports, the vast majority of pancreatic IOPN patients undergo open surgery, whereas laparoscopic surgery has hardly been reported. Compared with traditional open surgery, laparoscopic surgery boasts advantages like reduced trauma, smaller incisions, less blood loss, and quicker recovery[8]. Minimally invasive surgery represents the trend in surgical development. Owing to the complexity and safety considerations of pancreatic surgery, the adoption of minimally invasive techniques in pancreatic surgery has progressed more slowly than in other surgical fields. Recent research indicates that, once the learning curve is overcome, laparoscopic minimally invasive pancreatic surgery is both safe and viable, and can yield treatment outcomes comparable to those of open surgery[9,10]. Nonetheless, this report presents two cases of pancreatic IOPN that were treated with laparoscopic surgery.

CASE PRESENTATION

Chief complaints

Case 1: The patient was a 60-year-old female who was admitted to the hospital on May 1, 2024 due to a pancreatic mass discovered half a month prior.

Case 2: A 61-year-old female was admitted to the hospital on March 11, 2024 due to a pancreatic mass found 5 days prior.

History of present illness

Case 1: Two weeks before admission, the patient underwent surgical treatment for a lower limb fracture at another hospital. During that period, a chest computed tomography (CT) scan revealed an occupying lesion in the body and tail of the pancreas. A subsequent abdominal enhanced CT scan suggested an occupying lesion in the body of the pancreas, possibly a neuroendocrine tumor. The patient attended our hospital for further evaluation and treatment. No symptoms such as abdominal pain, bloating, nausea, vomiting, or dizziness was found.

Case 2: Five days before admission, the patient was being treated at another hospital for a urinary tract infection. B-ultrasound indicated a hypoechoic lesion in front of the right side of the pancreas. The patient showed no discomfort such as abdominal pain or bloating.

History of past illness

Case 1: The patient had no history of abdominal surgery, smoking, or alcohol consumption.

Case 2: She had a history of cholecystectomy and hypertension.

Personal and family history

All other personal and family medical history was noncontributory.

Physical examination

Case 1: No jaundice of the skin or sclera. The abdomen was soft, with no tenderness or rebound tenderness in the upper abdomen. No abdominal mass was palpable. Murphy's sign was negative and shifting dullness was negative. Bilateral renal punch was negative. The left lower limb was fixed with a brace.

Case 2: No jaundice of the skin or sclera. The abdomen was soft, without tenderness or rebound tenderness in the upper abdomen. No abdominal mass was palpable. Murphy's sign was negative. Shifting dullness was negative. Bilateral renal punch was negative.

Laboratory examinations

Case 1: Blood routine, biochemistry, tumor markers, *etc.*, were all normal.

Case 2: Blood routine and biochemistry results were normal. Carbohydrate antigen (CA) 19-9 was 204.91 U/mL.

Imaging examinations

Case 1: Abdominal enhanced CT indicated a mass in the tail of the pancreas. The mass had a clear boundary and was approximately 30 mm in size. A neuroendocrine tumor was highly suspected. Abdominal enhanced magnetic resonance (MR) indicated a cystic-solid mass in the pancreatic tail, with an uneven T2 signal. The diffusion weighted imaging signal was high and the apparent diffusion coefficient showed partially low-level signal. The boundary was clear, with a maximum section size of about 35 mm × 32 mm. After contrast enhancement, the solid portion of the mass was enhanced. The lesion appeared to be connected to the pancreatic duct (Figure 1A-D). MR imaging suggested a high possibility of a low-grade malignant tumor.

Case 2: Abdominal enhanced CT suggested an occupying lesion in the pancreaticoduodenal space, possibly indicating a gastrointestinal stromal tumor. Abdominal enhanced MR revealed an occupying lesion in the head of the pancreas, raising suspicion of a solid pseudopapillary tumor or neuroendocrine tumor (Figure 1E-H). Moreover, preoperative endoscopic ultrasonography also suggested an occupying lesion in the head of the pancreas. Puncture pathology revealed mucinous substances, inflammatory cells, histiocytes, and a small amount of glandular epithelium.

FINAL DIAGNOSIS

Case 1

Postoperative routine pathology indicated an IOPN in the body and tail of the pancreas with high-grade intraepithelial neoplasia. The immunohistochemistry results revealed positive *MUC6*, positive *MUC5AC*, negative *MUC2*, and positive hepatocyte paraffin 1 (HepPar1) and cluster of differentiation (CD) 117 (Figure 2A-F).

Case 2

Histological type: IOPN with focal microinvasion and proliferating nest-like neuroendocrine cells in the cyst wall. Immunohistochemistry results showed positive *MUC6*, positive *MUC5AC*, negative *MUC2*, and positive synaptophysin (Syn) and cytokeratin pan (CK-P) (Figure 2G-L).

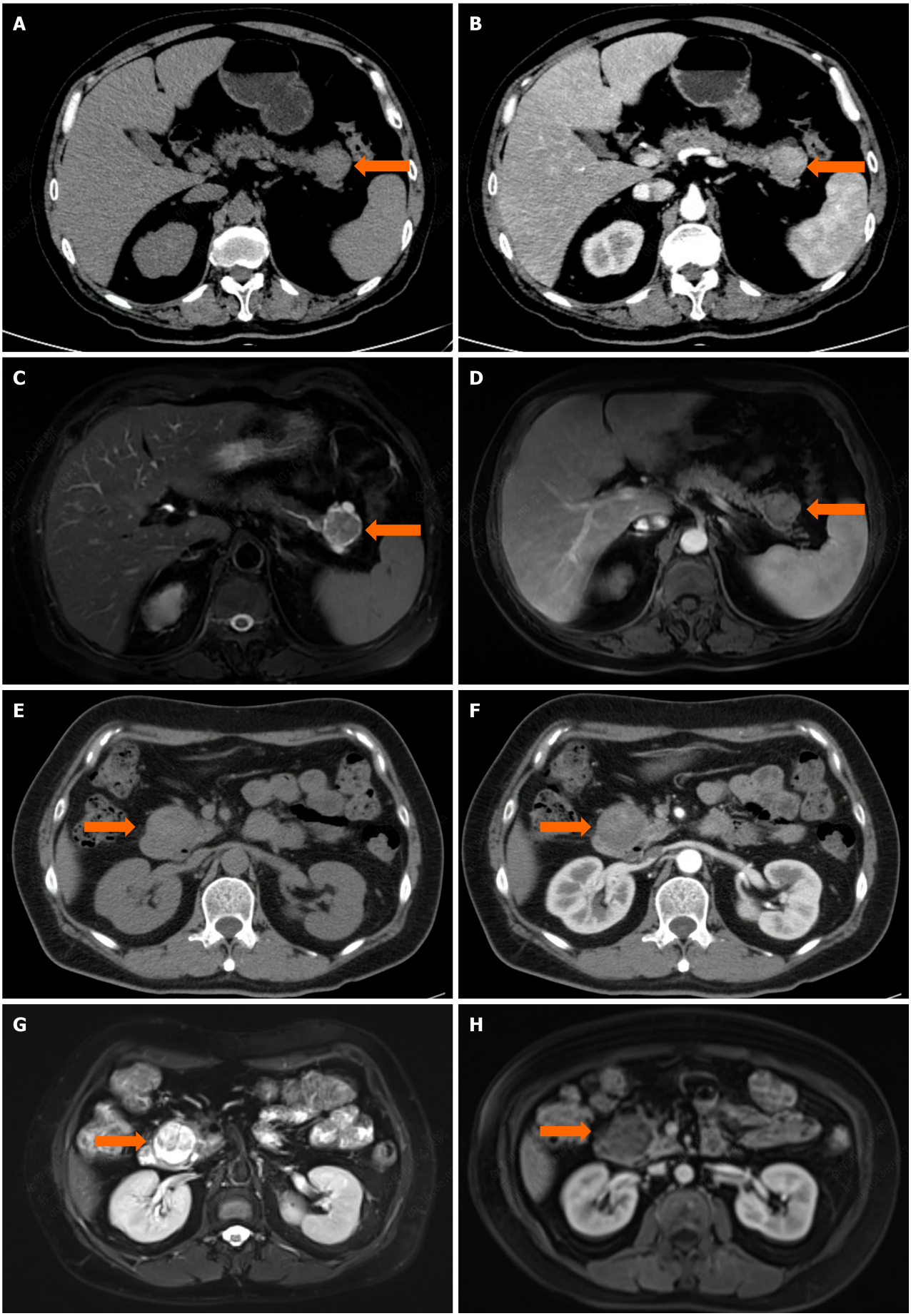


Figure 1 Computed tomography and magnetic resonance imaging. A-D: Case 1; Plain computed tomography (CT) scan shows a round soft tissue

shadow in the tail of pancreas with clear boundary and a diameter of 3 cm (orange arrow) (A); Contrast-enhanced CT of abdomen shows a persistent enhancement pattern within the tumor (orange arrow) (B); The T2-weighted image reveals uneven tumor signals, manifesting as a high signal at the edge and a low signal at the center (orange arrow) (C); Contrast-enhanced T1-weighted image clearly displays a mass, with an approximate dimension of 35 mm × 32 mm, that is prominently observable at the pancreatic tail (orange arrow). The solid part of the tumor exhibits enhancement and appears to possess a connection to the pancreatic duct (D); E-H: Case 2; Plain CT scan shows a nodular slightly higher density lesion in the pancreatic-duodenal space, with a clear boundary. The tumor diameter is approximately 3.5 cm (orange arrow) (E); Contrast-enhanced CT of abdomen shows an unevenly enhanced tumor with marked enhancement in the arterial phase, followed by a reduction in enhancement, and an indistinct boundary with the local part of the duodenum (orange arrow) (F); The T2-weighted image reveals that the majority of the tumor exhibits a high-intensity signal, whereas the central portion displays a low-intensity signal (orange arrow) (G); Contrast-enhanced T1-weighted image clearly shows significant edge enhancement (orange arrow) (H).

TREATMENT

Case 1

After completing preoperative preparations, the patient underwent laparoscopic distal pancreatectomy and splenectomy. Intraoperative rapid pathology indicated pancreatic mucinous adenocarcinoma. Consequently, a residual pancreatic resection was performed on the left side of the portal vein, accompanied by retroperitoneal lymph node dissection. Upon dissecting the specimen, the tumor was found to be located in the tail of the pancreas, showing a grayish-white appearance with a maximum diameter of 3.5 cm (Figure 3). The operation lasted for 342 minutes and the intraoperative blood loss was approximately 100 mL.

Case 2

After meticulously completing preoperative preparations, laparoscopic pancreaticoduodenectomy was performed on March 20, 2024. The tumor in the head of the pancreas was measured at 4.5 cm × 3.6 cm × 1.8 cm during postoperative pathology. The operation lasted for 431 minutes with an intraoperative blood loss of approximately 50 mL.

OUTCOME AND FOLLOW-UP

Case 1

The patient was discharged on postoperative day 8 with an excellent postoperative course. No recurrence was observed during the 8-month postoperative follow-up. The patient is entirely competent to engage in normal life and work activities, and expresses profound contentment with the therapeutic efficacy. Considering the potential for recurrence or malignant transformation of pancreatic IOPN, we recommend that patients undergo an abdominal enhanced CT examination every six months after surgery. Additionally, we will conduct continuous tracking.

Case 2

The patient exhibited an excellent postoperative course and was discharged on postoperative day 24. Two months after the surgery, the tumor marker CA19-9 dropped to the normal level. No recurrence was observed during the 10-month postoperative follow-up. The patient is entirely competent to engage in normal life and work activities, and expresses profound contentment with the therapeutic efficacy. Considering the potential for recurrence or malignant transformation of pancreatic IOPN, we recommend that patients undergo an abdominal enhanced CT examination every six months after surgery. Additionally, we will conduct continuous tracking.

DISCUSSION

IOPN shows similar clinical manifestations to those of IPMN, including abdominal pain, bloating, and jaundice. Approximately 30% of patients are asymptomatic, and the tumor is detected incidentally during imaging examination[11,12]. In terms of laboratory tests, no specific markers indicate the presence of this disease, although a few patients may show elevated CEA and CA19-9 Levels[13-15].

IOPN is more common in middle-aged and elderly individuals and can occur in any part of the pancreas, with a higher prevalence in the pancreatic head. IOPN demonstrates varying imaging characteristics and may present as cystic, cystic-solid, or solid lesions, which is similar to IPMN. Currently, only a few reports have explored the imaging differentiation between IOPN and other pancreatic tumors. Therefore, preoperative diagnosis remains extremely challenging. Wang *et al* [16] summarized 66 cases of IOPN reported in the literature. Among these, only 8 cases were correctly diagnosed as IOPN preoperatively, 14 cases were diagnosed as IPMN, 13 as pancreatic ductal adenocarcinoma (PDAC), 10 as mucinous cystic neoplasm, and 1 as a neuroendocrine tumor. Most patients with IOPN undergo surgical treatment as they have been diagnosed with conditions like IPMN and PDAC. Surgical methods include pancreaticoduodenectomy, duodenum-preserving pancreatic head resection, distal pancreatectomy and splenectomy, total pancreatectomy, *etc*[17]. In this report, for case 1, the preoperative diagnosis was considered neuroendocrine tumor? For case 2, the preoperative diagnoses were considered to be stromal tumor? Solid pseudopapillary tumor? Neuroendocrine tumor? This is similar to the previously reported results. Interestingly, all the suspected diseases under consideration required surgical resection, which made the

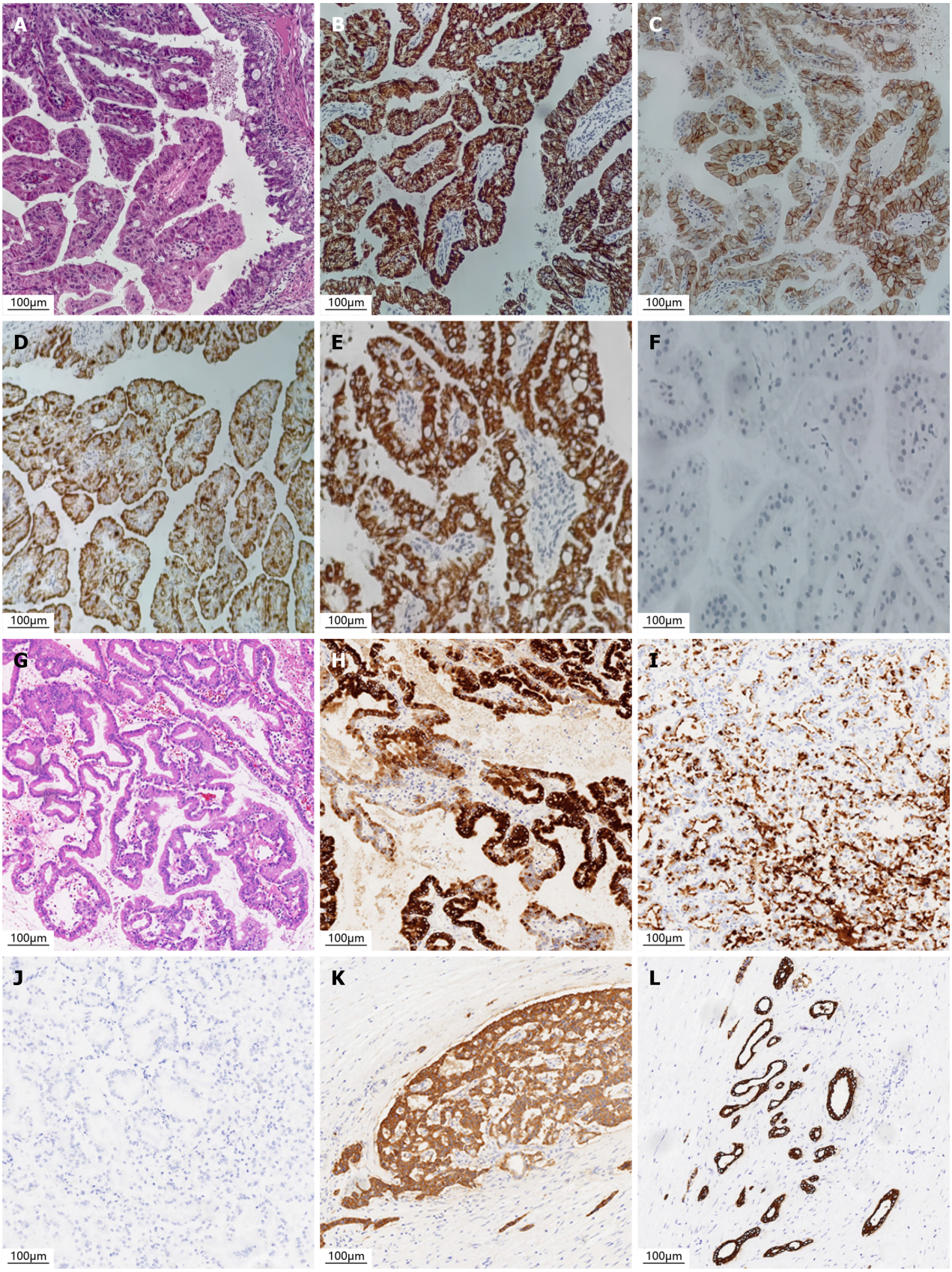


Figure 2 Hematoxylin-eosin stain and immunohistochemical results. A-F: Case 1; Hematoxylin-eosin stain of intraductal oncocytic papillary neoplasm (IOPN) (magnification: × 100) (A); Immunohistochemical results show that the tumour cells are positive for hepatocyte paraffin 1 (B); Cluster of differentiation 117 (C); *MUC5AC* (D); *MUC6* (E); Negative for *MUC2* (magnification: × 100) (F); G-L: Case 2; Hematoxylin-eosin stain of IOPN (magnification: × 100) (G); Immunohistochemical results show that the tumour cells are positive for *MUC6* (H); *MUC5AC* (I); Negative for *MUC2* (J); Positive for synaptophysin (K); Cytokeratin pan (magnification: × 100) (L).



Figure 3 The surgical specimen after resection (case 1). The tumor is grayish-white to the naked eye, with a maximum diameter of 3.5 cm.

surgical indications definitely clear. Notably, positron emission tomography (PET)-CT may facilitate the preoperative diagnosis of IOPN. Literature reports that the standard uptake value of IOPN on PET-CT is much higher than that of general pancreatic cancer. Therefore, PET-CT is a potential diagnostic method for preoperative differentiation[18], which may be attributed to eosinophilic cells being highly active in metabolism, and non-pancreatic oncocytomas also showing strong positive manifestations on PET-CT[19,20]. However, it's a pity that neither of the two patients in this report underwent a complete PET-CT examination before surgery. In the future, for similar pancreatic tumor patients with unclear preoperative diagnoses, a PET-CT examination can be completed. In the future, we will devote more efforts to studying the role and value of PET-CT in the diagnosis of IOPN. If the preoperative diagnosis can be made more definite, both doctors and patients will be able to face the situation more calmly.

Currently, the differentiation between IOPN and IPMN mainly relies on pathological examinations. Adsay *et al*[1] reported that IOPN has an average diameter of 6.0 cm (1.6 cm-15.0 cm). Tumors usually grow in or are connected to the dilated pancreatic duct, presenting as a cystic or cystic-solid lesion. Grayish-white or grayish-brown, soft, and fragile papillae can be seen in the cyst, or may also appear as grayish-white nodules attached to the wall. However, if the tumor cells grow in a solid form, the dilated pancreatic duct structure may not be obvious, hindering the identification of intraductal lesions through imaging and macroscopic observation. In addition, IOPN generally produces less mucus than other types of IPMN[21]. Under low magnification, a significant difference between IOPN and IPMN is that most tumor cells contain abundant eosinophilic granules in their cytoplasm. However, the mucus differentiation of IOPN is often not obvious, and goblet cells containing mucus or epithelial luminal spaces containing mucus are commonly observed between tumor cells, forming a sieve-like structure. The nuclei of IOPN tumors are round or oval in shape, displaying obvious atypia, such as mitotic figures, nuclear pleomorphism, coarse chromatin, and prominent nucleoli, *etc*. Based on its complex structure (complex branching papillae) and nuclear atypia, all IOPN are accompanied by high-grade dysplasia, which is not found in IPMN[22]. Approximately 30% of IOPN may be accompanied by associated invasive carcinomas. The invasive carcinomas have the characteristics of eosinophilic cells similar to those of the intraductal tumors[23]. Wang *et al*[16] summarized the pathological characteristics of 66 patients with pancreatic IOPN from 24 published literatures. The results revealed that all 66 patients had severe dysplasia or invasive carcinoma; specifically, 59% showed severe dysplasia and 41% showed invasive carcinoma. In this report, case 2 demonstrated invasive carcinoma components. IOPN generally exhibits an excellent prognosis. Notably, even in cases where it is complicated by invasive carcinoma, the 5-year survival rate remains 100%, and the 10-year survival rate stands at 94%. When performing surgical resection, it is necessary to ensure a negative surgical margin to reduce the risk of recurrence. Intriguingly, recurrence can sometimes occur as late as 10 years following the mass resection. However, even if such a recurrence does transpire, the prognosis following re-operation remains highly promising[7]. The two patients in this report were followed up for only 8 months and 10 months respectively. The follow-up period is still too short. In the future, we will continue to follow up these two patients. It is recommended to conduct an enhanced abdominal CT examination every six months.

Similar to IPMN, IOPN typically shows positive results for cytokeratin 7, cytokeratin 8, cytokeratin 18 and cytokeratin 19. However, positive *MUC6* and *MUC5AC*, and negative for *MUC2* are also observed, which can be used to differentiate between IPMN and IOPN. Meanwhile, HepPar1 and CD117 may also show positive expressions in IOPN[24,25]. In these two cases, immunohistochemical staining revealed positive expressions of *MUC6* and *MUC5AC*, while the expression of *MUC2* was negative, which helped to rule out the possibility of other tumors and further confirmed the diagnosis of IOPN. In case 1, both HepPar1 and CD117 exhibited positive expressions. In case 2, immunohistochemistry results showed positive results for Syn and CK-P, which were immunohistochemical markers representing neuroendocrine

differentiation and microinvasion respectively.

The PubMed database was searched, revealing a case diagnosed with IOPN of the pancreas with prominent invasion that was treated with laparoscopic pancreatosplenectomy, proximal gastrectomy, and transverse colectomy. This was the first and only case reported by Nomaru *et al*[26] in 2023, and all the other reported cases underwent opensurgeries. Previous reports have focused on the pathological features and diagnosis of IOPN. Compared with open surgery, laparoscopic pancreatic surgery has advantages such as less intraoperative bleeding and faster postoperative recovery[27,28]. Moreover, it will not augment the incidence of complications, including postoperative infection and intra-abdominal bleeding[29]. However, whether these advantages are applicable to pancreatic IOPN remains unknown, and this requires research with a larger sample size.

The pancreas is located deep in the body, surrounded by numerous large blood vessels, and often involves reconstruction after resection, which makes the surgery highly challenging. Therefore, the application of laparoscopic surgery in pancreatic operations lagged behind that of organs such as the gastrointestinal tract and liver. Previously, we had an adequate reserve of laparoscopic techniques and were proficient in performing laparoscopic radical gastrectomy and liver cancer resection. Without sufficient technical reserves, one should refrain from carrying out laparoscopic pancreatic surgery. At the same time, laparoscopy offers an excellent field of view and magnification effect, enabling more precise operations. Compared with open surgery, laparoscopic surgery may achieve more thorough lymph node dissection and a higher R0 resection rate[30,31].

The current report presents two cases of patients with pancreatic IOPN treated by laparoscopic surgery, including one case of laparoscopic pancreaticoduodenectomy and one case of laparoscopic distal pancreatectomy and splenectomy. Both of our patients were discharged smoothly after surgery without complications such as bleeding, pancreatic fistula, or reoperation. The patients and their family members were very satisfied with the treatment outcomes. The two patients had a good prognosis and developed no recurrence during the follow-up period. Therefore, laparoscopic surgery for pancreatic IOPN is a safe and effective method. Nevertheless, further research is required to confirm these findings. Therefore, we recommend that hospitals with rich experience in laparoscopic surgeries can attempt laparoscopic surgery for pancreatic IOPN.

However, this study still has some limitations. The main limitation is that only two patients were included, resulting in a small sample size, which prevents relevant statistical analysis. We hope to include more IOPN patients in future studies to conduct further research on the differentiation of IOPN from other pancreatic tumors, as well as studies on the laparoscopic and open surgical treatments for IOPN.

CONCLUSION

IOPN of the pancreas is extremely rare. The clinical manifestations, laboratory examinations, and imaging findings are all atypical, making preoperative diagnosis difficult. Thorough histopathological and molecular analysis is essential for an accurate diagnosis. Surgery is the preferred treatment, and while a certain proportion of cases may be associated with invasive cancer, the surgical prognosis remains favorable. Neither of the two patients had perioperative complications or recurrence. Laparoscopic surgery can be considered as one of the treatment options for IOPN of the pancreas. Certainly, this requires verification with more cases and long-term follow-up.

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FOOTNOTES

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LETTER TO THE EDITOR

Important issues on the prevention of surgical site infections and the management of prophylactic antibiotics

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Abstract

In this article, we have addressed the recent published article by Wang *et al* which examines risk factors associated with surgical site infections (SSIs) and evaluates the effectiveness of prophylactic antibiotics in their prevention. Wang *et al* identified several significant risk factors of SSIs, including age ≥ 60 years, diabetes mellitus, and surgical complications such as insufficient cystic duct stump closure, gallbladder perforation, empyema, and postoperative hematoma. Their findings suggest that prophylactic antibiotics can serve as a protective factor against SSIs. However, other reported risk factors and preventive strategies warrant consideration to further reduce the incidence of SSIs, lower healthcare costs, and enhance patient outcomes. Additionally, the judicious use of prophylactic antibiotics is crucial in light of the growing global challenge of antibiotic resistance caused by the misuse and overuse of antibiotics. Effective management strategies for prophylactic antibiotic use should be prioritized to balance infection control with the need to combat antimicrobial resistance.

Key Words: Surgical site infections; Prophylactic antibiotics; Risk factors; Preventive measures; Management

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Core Tip: The occurrence of surgical site infections is associated with patient's characteristics and surgical factors. Preventive strategies such as risk assessment, disinfection, and enhanced nutrition are essential to reducing the incidence of surgical site infections and healthcare expenditures and improving patient's clinical outcome. In addition, the use of prophylactic antibiotics should be individualized and precise.

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TO THE EDITOR

We read with great interest the recent article by Wang *et al*[1] entitled "Evaluating risk factors for surgical site infections and the effectiveness of prophylactic antibiotics in patients undergoing laparoscopic cholecystectomy", which demonstrated that age, diabetes, and certain surgical complications could impact the occurrence of surgical site infections (SSIs) in patients undergoing laparoscopic cholecystectomy based on a retrospective analysis, highlighting that effective management of these factors and the use of prophylactic antibiotics can reduce the incidence of SSIs. Surgical incisions often expose sterile tissues to the outside environment which make it difficult to prevent contamination[2]. This is a common and serious complication occurring after surgery, with a global incidence of 2%-3% and up to 20% of some iatrogenic infections, which together have a significant negative impact on patient recovery and the global healthcare system, especially in the context of increasing antibiotic resistance and increased surgical complexity[3]. In recent years, although the incidence of SSIs has reduced to a certain extent with the advancement in aseptic technique and optimization of perioperative antibiotic management, the prevention and control of SSIs continues to face several difficulties.

INFLUENCING FACTORS OF SSI'S

Individual factors

Extensive research has identified advanced age, obesity, and tobacco use as significant risk factors for SSI development[4,5]. The Asia Pacific Society of Infection Control Guidelines for SSI prevention also highlight these factors, defining older age as 65 years and above[6]. Wang *et al*[1] similarly observed a heightened risk of SSIs in older patients, attributing this to a weakened immune response and reduced physiological reserve. Additionally, preoperative metabolic abnormalities play a critical role in increasing SSI risk. A meta-analysis of 13 million individuals found that metabolic syndrome is associated with a significantly elevated risk of all types of SSIs (odds ratio = 1.64; 95% confidence interval: 1.52-1.77; $P < 0.01$)[7]. Obesity, particularly with a body mass index (BMI) ≥ 35 kg/m², has also been shown to increase SSI risk, as evidenced in a retrospective study on abdominal wall reconstruction patients[8]. The role of preoperative comorbidities, especially diabetes mellitus, is critical. Wang *et al*[1] emphasized the importance of stringent perioperative glycemic control, as poor preoperative glycemic management are well-documented high-risk factors for SSIs. Long-term hyperglycemia reduces the body's immunity and fosters high-sugar conducive to microbial growth[6,9]. Hypertension is another comorbidity associated with SSI risk[10,11]. Poorly managed hypertension increases the likelihood of intraoperative bleeding, complicates surgical procedures, and impairs wound healing due to long-term vascular changes. Other conditions, such as chronic obstructive pulmonary disease, further elevates SSI risk. Long-term glucocorticoid use in chronic obstructive pulmonary disease patients can lead to immune dysfunction[12]. Peripheral vascular disease and coronary artery disease are also significant risk factors, likely due to impaired white blood cell chemotaxis[13,14]. Approximately 70%-95% of SSI are attributed to the patient's endogenous flora[15]. Additional factors, such as recent radiotherapy and a history of skin or soft tissue infections, may disrupt the patient's microbiome and immunity, further increasing SSI risk[6].

Surgery-related factors

Surgical complexity, prolonged operation time, and intraoperative blood loss are key contributors to the incidence of SSIs. Schlager *et al*[16], in a review of 25928 surgical procedures across 15 observational studies, reported higher SSI rates in cases involving local flaps and skin grafting. A separate meta-analysis of 32 studies identified complex operations, such as deficit repairs, neck dissections, mandibular surgeries, tracheostomies, as significant risk factors[17]. Laparotomy and blood transfusion have been consistently associated with increased SSI risk[17-19]. Patients with a history of surgeries face an elevated likelihood of developing adhesions, which can complicate subsequent procedures, extend operation times, and heighten SSI risk. For example, a meta-analysis of 23 studies identified prior knee surgery and the use of

hamstring autografts as risk factors for SSIs following anterior cruciate ligament reconstruction[5].

Medications

The use of medications such as steroids, immunosuppressants, and biologics is associated with an increased risk of infection due to their immunosuppression properties[5,16]. Clindamycin, an antibiotic, has been identified as a significant risk factor for SSIs in patients with head and neck cancer[17]. Conversely, perioperative antibiotics have been shown to significantly reduce the risk of SSIs, particularly in high-risk procedures such as abdominal surgeries and organ transplants[20]. However, inappropriate use of perioperative antibiotics can elevate the risk of SSIs. A multicenter randomized controlled trial in Japan found that intravenous antibiotics alone, without preoperative oral antibiotic prophylaxis, were associated with higher SSI rates during laparoscopic colon surgery[21]. Indiscriminate or improper antibiotic use has further exacerbated the emergence of drug-resistant bacterial strains, making antibiotic resistance a critical public health concern. Studies have indicated that over-reliance on broad-spectrum antibiotics, especially prolonged postoperative use, significantly increases the prevalence of drug-resistant infections[22].

Preoperative nutritional status

Nutritional deficiencies are a key risk factor for SSIs. Chen *et al*[18] analyzed published studies on gastric cancer patients and found anemia and hypoproteinemia were significant contributors to SSI risk. Additionally, BMI < 20 kg/m^2 was identified as a major risk factor for SSIs in head and neck cancer patients[17]. A meta-analysis by Xie *et al*[23], involving 24 studies and 179388 patients, confirmed that malnutrition is a significant predictor of SSIs (odds ratio = 1.811; 95% confidence interval: 1.512-2.111; $P < 0.001$). Similarly, a review on spinal surgeries revealed that malnourished patients, particularly those undergoing thoracolumbar or sacral procedures, are more prone to SSIs[24]. To mitigate these risks, the European Society for Clinical Nutrition and Metabolism recommends early preoperative nutritional support and supplementation for malnourished surgical patients, which can effectively reduce SSI risk[25].

PREVENTION STRATEGIES OF SSI'S

Risk prediction

The American Society of Anesthesiologists (ASA) score is a widely used classification system developed by the United States Society of Anesthesiologists for surgical patients. This system is used to predict perioperative risks based on patients' physical status and surgical factors, including BMI and comorbidities. An elevated ASA score has been consistently associated with an increased risk of SSIs[26]. Patients with high ASA scores should be closely monitored and provided with individualized care. The United States Centers for Disease Control and Prevention (CDC) uses the National Healthcare Safety Network for SSI surveillance. A study employing stepwise logistic regression on National Healthcare Safety Network data developed risk-specific models by surgical type, improving the predictive accuracy of SSI risk[27]. Similarly, Wang *et al*[1] utilized univariate and multivariate logistic regression to identify risk factors for laparoscopic cholecystectomy, tailoring a predictive model for laparoscopic procedures. Preoperative laboratory tests can provide valuable insights into SSI risk. Key markers include preoperative albumin < 3.5 mg/dL, total bilirubin > 1.0 mg/dL, and hemoglobin A1c level of ≥ 8%, indicating poorly controlled diabetes, requires immediate attention[6]. Additionally, inflammation-related markers should be monitored to detect potential infections early, enabling timely interventions to reduce SSI risk.

Surgical management

Effective SSI prevention requires meticulous management across the preoperative, intraoperative, and postoperative stages. The operating room environment and equipment must adhere to stringent hygiene standards, with thorough cleaning and disinfection of the surgical area prior to the procedure[9]. Nurses should ensure proper preparation by organizing surgical tools and dressings, verifying counts, and supporting the surgical team efficiently. Adherence to aseptic techniques and robust postoperative wound care are essential components of infection control[28]. Clinicians must also monitor and regulate patient's body temperature and positioning during surgery to minimize complications. Emerging infection prevention strategies, such as antibacterial drug coatings and advanced disinfectants, are proving effective. For instance, antibacterial coatings can significantly reduce postoperative infection rates, particularly in high-risk surgeries such as orthopedic and neurosurgical procedures[29]. Antimicrobial-loaded cement and beads have been instrumental in managing infections in orthopedic surgeries[30]. Silver- and iodine-based dressings are widely used for their potent antibacterial properties[31]. Dialkylcarbamoyl chloride-coated dressings have shown promise in reducing SSIs, as indicated by a systematic review of 17 studies involving 3408 patients[32]. Similarly, antibiotic-coated absorbable sutures, such as triclosan-coated sutures, are increasingly employed in surgeries to lower bacterial loads and promote wound healing. These have proven especially effective in abdominal surgeries and are recommended in guidelines by the CDC and the World Health Organization[33-35].

Optimization of antibiotic use

The administration of surgical antibiotic prophylaxis within 120 minutes before surgery is a cornerstone of SSI prevention [36]. The effectiveness of prophylactic antibiotics in reducing SSIs is supported by the article under discussion[1]. For adult patients undergoing elective colorectal surgery, a combination of mechanical bowel preparation and oral antibiotics, in addition to standard intravenous antibiotic prophylaxis, is recommended[36]. Postoperative surgical

antibiotic prophylaxis duration should be determined by the type of surgery, with most guidelines advocating a maximum duration of 24 hours[36].

Recent studies emphasize the importance of individualized prevention strategies, tailored to the surgical site and the patient's health status. Common pathogens associated with SSIs include *Staphylococcus aureus* (*S. aureus*), coagulase-negative staphylococci (CoNS), and *Escherichia coli*[33,37]. Targeted antibiotic regimens, based on surgical type and patient factors, significantly improve SSI prevention[37,38]. For *S. aureus*, first-generation cephalosporins and antistreptococcal penicillin are commonly used[33]. Preoperative nasal decolonization with intranasal mupirocin ointment, combined with or without chlorhexidine gluconate soap, is recommended for carriers[35]. However, methicillin-resistant *S. aureus* (MRSA) poses a significant challenge due to its resistance to most β-lactam antibiotics through a change in the properties of penicillin-binding proteins[39]. In cases of MRSA colonization or high institutional MRSA rates, vancomycin may be employed, though its usage must be strictly monitored to avoid resistance development[33,39]. CoNS species are increasingly resistant to common antimicrobials, including methicillin[40]. Although rare, resistance to vancomycin in CoNS has been reported, underscoring the need for the cautious use of this antibiotic to prevent resistant strains[41]. Surveillance data from the China Antimicrobial Resistance Surveillance System highlight the high resistance of *Escherichia coli* to quinolones (*e.g.*, levofloxacin and ciprofloxacin). Consequently, the perioperative use of these drugs should be regulated to limit resistance development[42]. The medical community is increasingly adopting individualized antibiotic treatment strategies based on etiological evidence. Studies have demonstrated the benefits of precise antibiotic selection through preoperative microbial culture and pathogenic testing (*e.g.*, multiplex PCR panels). This approach effectively reduces the incidence of SSIs, while alleviating the pressure of drug-resistant strain selection[43,44]. Additionally, hospital infection control committees play a critical role in supervising rational antibiotic use and minimizing unnecessary prescriptions. In the United States, the CDC has implemented a national hospital antimicrobial use and management model, introducing the standardized antimicrobial administration ratio. This tool quantitatively assesses prescribing practices, identifies areas for improvement, and evaluates the impact of interventions[45,46].

Enhanced nutritional support

Nutritional status is a critical determinant of surgical outcomes. Healthcare workers should use validated nutritional screening tools to identify malnutrition and provide targeted nutritional support[47]. Dietary guidance on adequate protein, vitamin, and mineral intake can improve immune function and overall health[9]. A retrospective study suggested that improving vitamin D levels can reduce SSI incidence[48]. For patients with a BMI of < 18.5 kg/m^2 undergoing major surgery, oral or enteral nutrient-enhanced formulas should be prioritized[36]. However, prophylactic feeding tube placement is not recommended, as it may harm the patient and delay procedures[36].

CHALLENGES

The coronavirus disease 2019 pandemic has posed unprecedented challenges to global healthcare systems, including SSI prevention and control. Disruptions in preoperative infection screening and postoperative infection management have complicated prevention efforts. However, measures such as enhanced hand hygiene and stricter disinfection protocols have contributed to reducing some infection risks[49]. Lessons from pandemic control efforts have driven improvements in operating room air purification systems and aseptic operation procedures, offering new perspectives on SSI prevention [50]. Developing predictive models tailored to specific patient populations is vital. Strategies should include epidemiologically significant infection definitions, stratified analyses of SSI risk factors, and effective data feedback mechanisms. The transition from generalized to individualized prevention measures is crucial, as patient-specific factors - such as immune status, genetic background, and pathogen characteristics - significantly influence the risk of infections[51]. Emerging genomics and multi-omics technologies are poised to revolutionize SSI prevention. These tools can identify susceptibility genes and biomarkers, enabling highly personalized preoperative risk assessments and precise infection control strategies.

CONCLUSION

Preventing SSIs and managing antibiotics are critical for surgical success, especially amid rising surgical complexity and antibiotic resistance. While Wang *et al*[1] effectively highlighted SSI risk factors, conventional preventive measures, and antibiotic challenges while proposing individualized, evidence-based approaches. Future research should integrate multi-omics technologies to develop personalized prevention programs. Rational antibiotic use, informed by precise microbial diagnostics, is vital to mitigate resistance and improve patient outcomes. Additionally, incorporating lessons from pandemic control - such as improved aseptic techniques and optimized preoperative screening - combined with robust nutritional support can significantly advance SSI prevention and control. By adopting these strategies, we can enhance postoperative outcomes and reduce the burden on global healthcare systems.

FOOTNOTES

Author contributions: Wang MK and Yang JS conceptualized, designed, and revised the manuscript; Yu XL and Peng JH drafted the

manuscript; Chang Q and Chen JW collected and summarized the literature. All authors have read and approved the final manuscript. Yu XL and Peng JH wrote the draft and contributed equally to this work as co-first authors. Both Wang MK and Yang JS conceptualized, proposed, and supervised the entire process of preparing this manuscript, and played important and indispensable roles in the manuscript preparation and revision as the co-corresponding authors. Wang MK applied for and obtained the funds for this research project. Wang MK conceptualized, designed, and supervised the entire process of the project. He searched the literature, and revised and submitted the early drafts of the manuscript. Yang JS was instrumental and responsible for the comprehensive literature search, preparation, and submission of the current version of the manuscript. This collaboration between Wang MK and Yang JS is crucial for the publication of this manuscript and other manuscripts under preparation.

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LETTER TO THE EDITOR

Central vascular ligation and complete mesocolon excision *vs* D3 lymphadenectomy: Standardization of surgical technique

Sung Uk Bae

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Abstract

Surgical advancements have transformed colorectal cancer treatment, with complete mesocolic excision (CME) becoming a crucial method to guarantee oncological safety and effectiveness. The article by Yadav emphasized the significance of CME in attaining optimal resection margins, thorough lymph node dissection, and enhanced long-term survival rates. The adjunctive function of D3 lymphadenectomy, emphasizing the clearance of lymphatic drainage along the supplying vessels, was also addressed. CME with central vascular ligation, based on the principles of total mesorectal excision for rectal cancer, entails *en bloc* tumor resection and precise dissection along the embryological planes, thus diminishing recurrence and improving survival rates. The viability and safety of minimally invasive techniques, such as laparoscopic CME, have been confirmed; however, technical difficulties remain owing to the intricate vascular anatomy. Robotic-assisted surgery presents potential benefits, including accurate lymphatic dissection and intracorporeal anastomosis. However, evidence demonstrating its superiority over laparoscopic techniques is scarce owing to high costs and prolonged duration. This study promotes the global standardization of CME as an essential element of modern colorectal cancer surgery. CME epitomizes contemporary oncological practices, requiring widespread adoption to achieve superiority in colon cancer management.

Key Words: Laparoscopy; Mesocolon; Colonic neoplasm; Lymph node; Surgical technique

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Core Tip: In this recently published manuscript, Yadav emphasized the complementary role of D3 lymphadenectomy, which enhances lymphatic drainage clearance, aligning with the goal of complete mesocolic excision (CME) to achieve R0 resection. The authors advocated for the global standardization of CME and its integration into surgical training to ensure equitable access and improved outcomes in patients with colon cancer. This underscores the role of CME as a cornerstone of modern oncological surgery, which is essential for achieving excellent colorectal cancer treatment.

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TO THE EDITOR

Surgical advancements in the evolving field of colorectal cancer treatment have consistently demonstrated their significance in improving patient outcomes. For example, complete mesocolic excision (CME) is a pivotal technique with redefined oncological safety and efficacy. The recent article authored by Yadav[1] and published in *World Journal of Gastrointestinal Surgery*, effectively emphasizes the pivotal significance of CME with D3 lymphadenectomy for attaining optimal resection margins and enhancing long-term survival rates in patients with colon cancer. The discourse on D3 lymphadenectomy is equally compelling, as it enhances CME by addressing lymphatic drainage along the principal feeding vessels. The techniques prioritize the common objective of achieving R0 resection while optimizing lymph node yield. The present study reconciles these two methodologies and demonstrates how CME and D3 dissection collaborate to yield enhanced oncological results.

The primary principle of colon cancer surgery is the removal of primary tumors and achievement of adequate surgical margins and locoregional lymph node dissection (Figure 1). CME with central vascular ligation (CVL) has been introduced as a treatment for colonic cancer, based on the concept of complete mesorectal excision for rectal cancer, which has resulted in a higher 5-year survival rate and a reduced recurrence rate[2-4]. Similar to the notion of total mesorectal excision, this technique entails the *en bloc* resection of the tumor and its surrounding soft tissues by sharply dissecting the visceral plane from the parietal fascia layer, as well as the entire regional mesocolon, as a singular and intact structure[5]. This surgical model offers reduced local recurrence and improved survival rates compared with conventional colectomy[3,6].

Some researchers in the field of surgery have introduced an equivalent lymphadenectomy principle that depends on tumor location and extent and defined the procedure as "modified CME with CVL"[7]. For malignancies that are in the early stages of development, the Japanese Society for Cancer of the Colon and Rectum suggests D2 resection, while D3 resection is recommended for more advanced disease[8]. Regarding the current lack of consensus on the precise boundaries in D2 *vs* D3 dissection, we acknowledge that this ambiguity arises from variations in surgical guidelines and practices across institutions and regions. As noted in our manuscript, the Japanese Society for Cancer of the Colon and Rectum defines D2 resection as the removal of pericolonic and regional lymph nodes and D3 dissection as the removal of lymph nodes along with the principal feeding vessels. This definition aligns with the broader goals of CME, which emphasize *en bloc* tumor resection with CME to optimize oncological outcomes. However, the integration of CME with D3 dissection remains under discussion. CME aims to achieve intact mesocolic resection along the embryological plane, ensuring comprehensive lymph node retrieval. In contrast, D3 dissection prioritizes systematic lymphadenectomy along the superior mesenteric vessels. Although these techniques share common oncological principles, their overlap and differentiation require further clarification. Despite the ongoing debate regarding the surgical extent of D3 lymphadenectomy and CME, we are of the opinion that these surgical techniques exhibit comparable oncological safety.

The feasibility and safety of the former have been demonstrated in numerous trials that compare standard laparoscopic and open CME for right-sided colon cancer. These trials have yielded satisfactory oncologic outcomes[9]. However, the execution of minimally invasive CME with CVL for right-sided colon cancer continues to be a difficult task. The feasibility and safety of the laparoscopic method were demonstrated in numerous studies that compared conventional laparoscopic surgery with open CME for right-sided colon cancer, resulting in acceptable oncologic outcomes[10-12]. Nevertheless, the minimally invasive approach to CME and CVL for right-sided colon cancer is difficult due to the complex variable vascular anatomy of the right colon and the technical limitations of laparoscopic instruments. Laparoscopic dissection of the lymph nodes surrounding the superior mesenteric vessels is particularly problematic.

Despite reports comparing the outcomes of laparoscopic CME and CVL, the overall adoption rate of laparoscopic procedures remains low. The intrinsic limitations of laparoscopic surgery were addressed by the development of a surgical robotic system, which was subsequently implemented in the colorectal domain to address the challenges associated with laparoscopic rectal cancer surgery in a constricted pelvic (Figure 2). However, it remains uncertain whether robotic surgery offers substantial clinical advantages over laparoscopic surgery in the treatment of colonic malignancy[13-17]. Robotic colectomy for right-sided colon cancer may provide several advantages. First, it facilitates secure and accurate lymphatic dissection along the superior mesenteric trunk. Second, this method facilitated appropriate mesocolic resection with improved visibility and consistent traction.

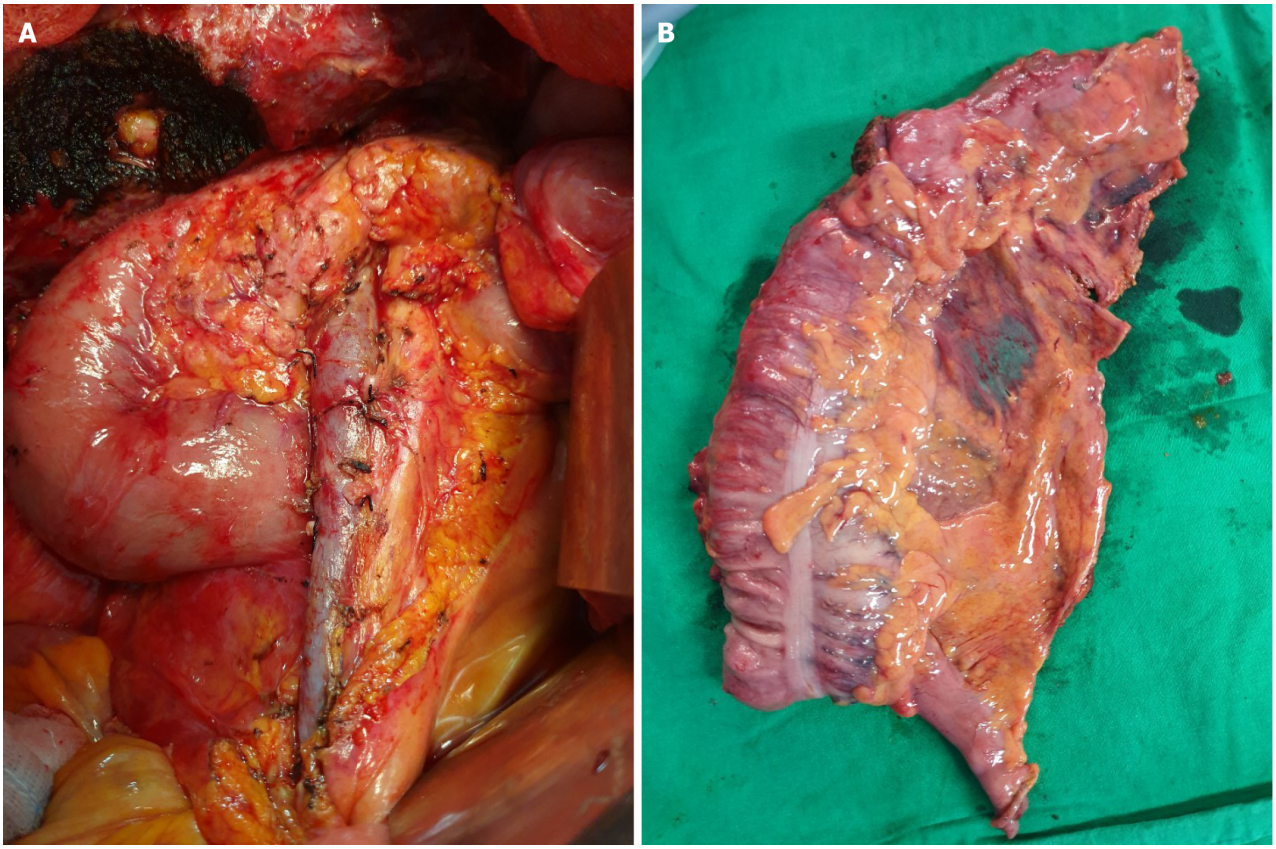


Figure 1 Open D3 right hemicolectomy. A: Intraoperative view following completion of open right hemicolectomy; B: Specimen examination of reduced-port robotic right hemicolectomy with D3 lymphadenectomy for an ascending colon carcinoma.

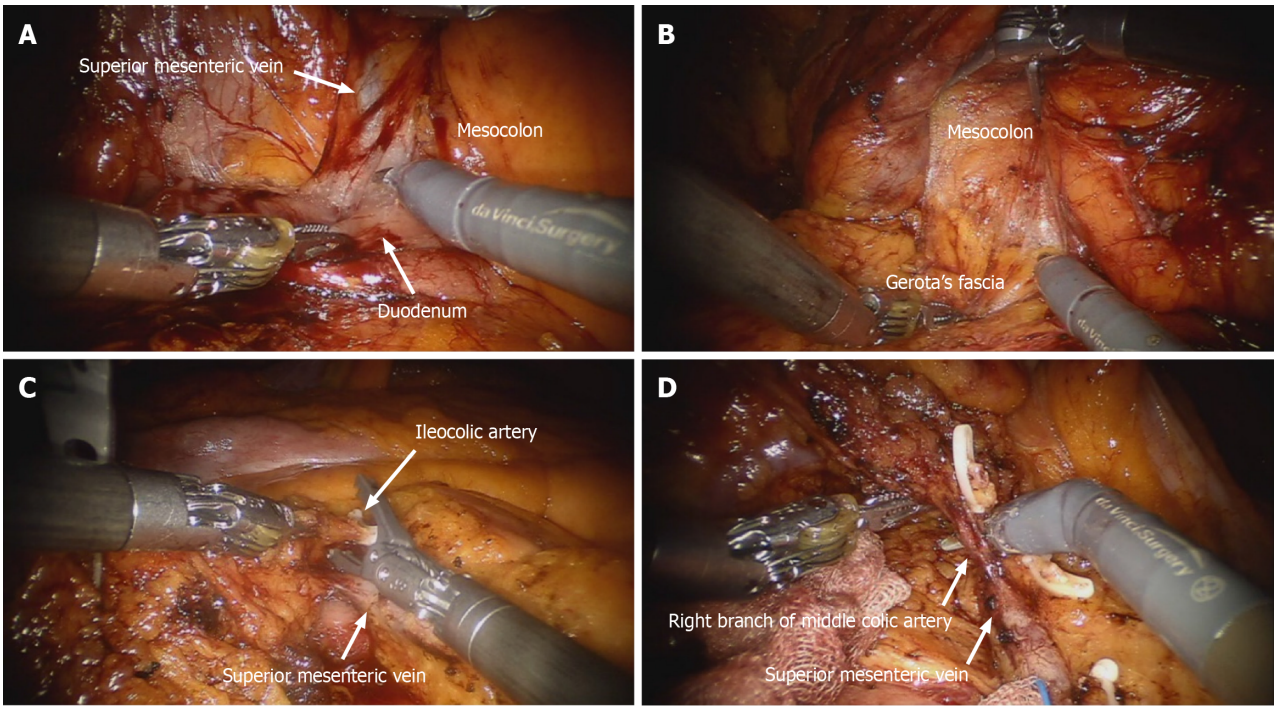


Figure 2 Intraoperative view of a robotic right hemicolectomy. A: Exposure of the distal segment of the duodenum and the pancreatic head; B: Sharp dissection between the peritoneal cavity and the mesocolon within the retroperitoneal space; C: Ligation of the ileocolic vessels using the wristed robotic advanced bipolar energy device; D: Dissection of the middle colic vessels.

Intracorporeal anastomosis was ultimately made feasible and secure by the robotic technique. Nevertheless, there is insufficient evidence to support the claim that robotic CME and CVL outperform laparoscopic surgery in terms of clinical and oncological outcomes. Park *et al*[18] conducted a randomized clinical trial to compare the clinical and long-term outcomes of robot-assisted and conventional laparoscopic right colectomy with CME and CVL. They found comparable results. Nonetheless, robotic colectomy was linked to extended surgical duration and increased costs, leading to the conclusion that its advantages did not justify the elevated expenditure. The robotic group demonstrated a substantially lower conversion rate, reduced duration of hospital stay, and diminished blood loss, as demonstrated by a recent meta-analysis by Tschann *et al*[19]. However, the long-term oncological outcomes were similar between the two groups. In their propensity score–matched prospective nonrandomized study, Ferri *et al*[20] conducted a cost-effectiveness analysis and identified no significant difference in total costs between the robotic and laparoscopic groups. In order to determine the advantages of robot-assisted colon surgery, it is imperative to conduct additional investigations and randomized trials that focus on specific primary endpoints, such as intracorporeal anastomosis, CME with CVL, and cost-effectiveness.

CONCLUSION

The ongoing refinement of colorectal cancer treatment by the surgical community underscores the importance of CME as a symbol of advancement. Its demonstrated efficacy coupled with its capacity to standardize and enhance outcomes worldwide makes it an essential component of contemporary oncological surgery. Yadav's work[1] serves as a reminder of the need to adopt evidence-based practices and standardize surgical strategies globally. CME is not simply a surgical procedure; rather, it embodies the pinnacle of contemporary oncological standards. The current challenge involves establishing it as a universal practice, integrating it into surgical education, and making it available to all patients irrespective of location. Overall, the future of colon cancer surgery remains promising.

FOOTNOTES

Author contributions: Bae SU designed and performed the research, analyzed the data, and wrote and revised the manuscript.

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